

Bond University

DOCTORAL THESIS

Preventing Overdiagnosis

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Award date:
2016

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Preventing Overdiagnosis

A thesis submitted in total fulfilment of the requirements of the degree of
Doctor of Philosophy

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February 2015

Summary

Background

Medicine's ability to help the sick is being challenged by its propensity to harm the healthy. As part of broader evidence and concern about too much medicine,[1] overdiagnosis is being increasingly recognised as a cause of harm and waste.[2] Overdiagnosis occurs when people are diagnosed with a disease that won't harm them, commonly as a result of screening programmes detecting non-progressive diseases, such as indolent cancers. More broadly defined, overdiagnosis happens when expanding disease definitions label more people with milder symptoms or at lower risks, for whom a label and treatment may do more harm than good.

Aims

The thesis aimed to research the nature and causes of overdiagnosis, the mechanisms by which disease definitions are expanding, public awareness of overdiagnosis, and possible policy responses.

Methods

Several different methods were employed for a range of related research. An initial scoping of the literature was undertaken to prepare an overview. A cross-sectional study investigated how influential expert panels were changing definitions of common conditions. Arising from the scoping and the study, chronic kidney disease was selected and examined according to an explicit template, to learn more about how controversial definitions are expanded and defended. A questionnaire was developed and piloted, and a national quantitative survey conducted. A qualitative study analysed themes emerging from community responses to an open-ended question about the meaning of overdiagnosis.

Results

The initial literature scoping identified considerable evidence for overdiagnosis and potential drivers.[3] The cross-sectional study found among 16 expert panel publications, 10 widened definitions, 1 narrowed, and for 5, it was unclear.[4] No panel reported on potential for overdiagnosis, and of those panels making disclosures, 75% of members had multiple financial ties to companies with direct interests in broadened patient populations, contrary to Institute of Medicine, IOM, recommendations.[5,6] The case study found against a backdrop of sustained criticism, the controversial expansion of chronic kidney disease was

repeatedly defended by conflicted experts.[7] The survey found a minority of respondents (10%) - including those screened for prostate,(18%) and breast cancer,(10%) - reported they'd been informed about overdiagnosis, and a majority(78%) felt it inappropriate disease-defining panels had ties to companies.[8] A qualitative analysis of responses to "what do you think the term overdiagnosis means?" found 40% of participants had approximate understandings, 24% thought it meant overuse, and none mentioned screening.[9]

Discussion and Implications

A greater sensitivity to the problem of overdiagnosis is required in running and reporting on primary studies of tests and treatments, the production of systematic reviews, and proposals to change disease definitions.[10] Findings of endemic conflicts in panels setting diagnostic thresholds, in direct contrast to IOM and public antipathy, suggest a need for more independent and representative panels, informed by evidence about benefits and potential harms, including overdiagnosis. Survey findings reinforce the need for more information about overdiagnosis, particularly with screening. Recommendations include: (i) synthesising existing overdiagnosis evidence into an accessible repository; (ii) further investigating expanding disease definitions; (iii) reforming disease definition processes; (iv) initiating new international collaborations to further understand and combat overdiagnosis.

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10. Moynihan R, Henry D, Moons KGM. Using Evidence to Combat Overdiagnosis and Overtreatment: Evaluating Treatments, Tests, and Disease Definitions in the Time of Too Much. *PLoS Med*. 2014;11(7): e1001655. doi:10.1371/journal.pmed.1001655

Declaration and Addendum

This thesis is submitted to Bond University in fulfilment of the requirements of the degree of *Doctor of Philosophy*. This thesis represents my own original work towards this research degree and contains no material which has been previously submitted for a degree or diploma at this University or any other institution, except where due acknowledgement is made.

Ray Moynihan is the sole author on the Introduction and Discussion chapters, 1 and 8, and lead author on all other chapters, which are substantially unchanged multi-author papers. The original research work underpinning all chapters was driven in every case primarily by Ray Moynihan, who also produced initial drafts of each manuscript, and managed all aspects of the collaborative research projects. None of the work submitted in this thesis was carried out before the PhD candidature.

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Acknowledgments

Immeasurable gratitude is owed to my indefatigable supervisors, Paul Glasziou and Jenny Doust, who have been a constant source of inspiration, encouragement, collegiality and support through the development and delivery of this thesis.

A special thank you goes to all my other colleagues at the Centre for Research in Evidence-Based Practice at Bond University, for their on-going enthusiasm for the thesis subject matter and their support and laughter, including, but not limited to, Chris Del Mar, Tammy Hoffmann, Rae Thomas, Elaine Beller, Chrissy Erueti and Sarah Thorning. I'd also like to acknowledge all the administrative, academic, management, library and other staff at Bond, who've helped facilitated my research, and helped make my time during the thesis so enjoyable and productive.

I'm also indebted to colleagues, collaborators and friends who've offered advice, encouragement and guidance, including David Henry, Geoff Morgan, Alexandra Barratt, Kirsten McCaffery, Jolyn Hersch and Brooke Nickel.

And finally, a very loving thank you to my partner Miranda Burne, for bearing with me through the running of this academic marathon, and to my new son Louis, for his smiles and laughter that helped to propel me across the finish line.

Peer-reviewed journal articles arising from this thesis

- Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. *BMJ*. 2012;344:e3502.
- Moynihan RN, Cooke GP, Doust JA, Bero L, Hill S, Glasziou P. Expanding disease definitions in guidelines and expert panel ties to industry: a cross-sectional study of common conditions in the United States. *PLoS Med*. 2013;10:e1001500. doi: 10.1371/journal.pmed.1001500
- Moynihan R, Glassock R, Doust J. Chronic kidney disease controversy: how expanding definitions are unnecessarily labelling many people as diseased. *BMJ*. 2013;347:f4298.
- Moynihan R, Henry D, Moons KGM. Using Evidence to Combat Overdiagnosis and Overtreatment: Evaluating Treatments, Tests, and Disease Definitions in the Time of Too Much. *PLoS Med*. 2014;11(7):e1001655. doi:10.1371/journal.pmed.1001655

Manuscripts in press

- Moynihan R, Nickel B, Hersch J, Beller E, Doust J, Compton S, et al. Public opinions about overdiagnosis: a national community survey. In Press, *PLOS ONE*, May 20, 2015.
- Moynihan R, Nickel B, Hersch J, Doust J, Barratt A, Beller E, et al. What do you think overdiagnosis means?: a qualitative analysis of responses from a national community survey of Australians. In Press, *BMJ Open*, 2015.

Conference presentations arising from this thesis

- Moynihan R. "Overdiagnosis and disease-definitions: challenges and opportunities for the Cochrane Collaboration", oral presentation at a symposium titled "Preventing Overdiagnosis: Challenges and opportunities for the Cochrane Collaboration". Cochrane Colloquium, Auckland, New Zealand, September 30 - October 3, 2012
- Moynihan R. "Too Much Medicine?" Opening keynote at conference titled "Diagnosis & Treatment: Too Much Medicine?" hosted by Hunter New England Local Health District, Newcastle, Australia, August 21, 2013
- Moynihan R. "Expanding disease definitions and expert panel ties to industry: a cross sectional study of common conditions in the United States", oral presentation, at "Preventing Overdiagnosis" conference, Dartmouth College, Hanover, New Hampshire, United States, September 10-12, 2013
- Moynihan R. "Preventing Overdiagnosis – can Cochrane and systematic reviews help?", oral presentation at the Cochrane Colloquium, Quebec City, Canada, September 19-23, 2013
- Moynihan R. "How can Shared Decision Making impact on overdiagnosis?" Oral presentation at "A Symposium on Shared Decision Making in Australia: Identifying research priorities and the next steps", Gold Coast, Australia, October 21, 2013
- Moynihan R. Oral presentation at session titled "Policy Reform Focus: The Role of Overdiagnosis in the (non)-sustainability of Health Care" at "The 9th National Eidos Public Policy Congress", Gold Coast, Australia, November 10-12, 2013
- Moynihan R. "Expanding Disease Definitions and Expert Panel Financial

Ties to Industry”, oral presentation at the “Gold Coast Health and Medical Research Conference”, Gold Coast, Australia, November 28-29, 2013

- Moynihan R. Oral presentation at a session titled “Medicalising Normality: what constitutes a real disease and the dangers of diagnostic inflation”, delivered at the Festival of Ideas, University of Melbourne, Melbourne, Australia, October 1-6, 2013
- Moynihan R. “A national survey of awareness and attitudes about Overdiagnosis” oral presentation prepared by Ray Moynihan and delivered by Professor Alexandra Barratt at the “Preventing Overdiagnosis” conference, University of Oxford, United Kingdom, September 15-17, 2014
- Moynihan R. “Overdoing it with disease definitions”, oral presentation at a session titled “Overmedicalisation” at the Australasian Medical Writers Association annual conference, Sydney, Australia, August 29-30, 2014
- Moynihan R. Invited to deliver plenary presentation at the “Preventing Overdiagnosis” conference, National Cancer Institute, Washington D.C., United States, September 1-3, 2015

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Chapter 1

Introduction

Ray Moynihan

Summary

This chapter introduces the problem of overdiagnosis, offers a brief description of the framework and approach for the thesis, provides a discursive review of the literature, outlines the thesis research aims and questions, and concludes with brief explanations of the thesis research projects, which feature in forthcoming chapters.

Background

The problem of overdiagnosis has been the subject of growing attention in the medical literature over recent decades. Narrowly defined, overdiagnosis happens when someone is diagnosed with a disease that would not have caused them harm, often as a result of undertaking screening, and can lead to unnecessary treatments and wasted health resources. [1] As a result of a growing body of increasingly rigorous research, we now know overdiagnosis happens regularly as a by-product of certain cancer screening programmes which seek to detect early cancers in the healthy population, some of which would never go on to cause symptoms or premature death.

Because there are on-going debates over how to precisely define overdiagnosis, and measure how often it occurs, there are wide variations in estimates of the magnitude of the problem. In addition there is a view that some degree of overdiagnosis is an inevitable risk of screening programmes which target the healthy,[2] and that attempts to reduce overdiagnosis should proceed with caution as they may come at the cost of increasing underdiagnosis. Notwithstanding these debates and views there is an established consensus within the literature that for cancer screening, overdiagnosis is a real risk, it is causing significant amounts of potentially avoidable harm, and requires much wider recognition and action from health professionals, policy-makers and the public.[3]

The literature also includes much research and broader discussion on examples of overdiagnosis unrelated to cancer and screening.[1] More broadly defined, overdiagnosis happens when disease definitions are expanded, diagnostic thresholds lowered or diagnostic processes changed in ways that label more and more people at low risk of future illness or with milder symptoms, for whom a disease label and subsequent treatment may do more harm than good. While extensive, and covering many conditions, this literature on non-cancer overdiagnosis has not generally developed the same level of rigorous or consistent methods, though there are important exceptions.[4] In this broader definition, the literature on overdiagnosis intersects with Ivan Illich's critique of the medicalisation of life,[5] more recent sociological research on medicalisation,[6] wider evidence and concern about overuse of tests and treatments,[7] and historical analysis of medical excess.[8] Counterbalancing medicine's many successes with the growing threat to human health posed by

that success, the celebrated medical historian Roy Porter noted in 1996 the problem of “diagnosis creep” and the “expansion of treatable illnesses.” Describing the increasing medicalisation of normal life events and the transformation of risks into diseases, Porter observed that “Doctors and ‘consumers’ alike are becoming locked within a fantasy...everyone has something wrong with them, everyone can be cured.”[8]

The literature featuring explicit concerns about the problem described as “overdiagnosis” dates back to at least the 1970s, though papers at this time were extremely rare. Chapter 2 of this thesis - published in *The BMJ* in 2012 and the result of an initial scoping of the overdiagnosis literature at the commencement of my thesis[9] - offers an overview of contemporary understandings and examples of overdiagnosis. It notes the different pathways to overdiagnosis, including via “incidentalomas”, explores several factors driving overdiagnosis and what responses might help prevent it. In this opening introductory chapter 1, I outline the framework and approach of the thesis, offer a comprehensive discursive review of the literature up until 2014, and close with my research aims and questions, and with brief explanations of the forthcoming chapters.

Framework and approach

Being based for the duration of my thesis as a senior research fellow at the Centre for Research in Evidence-Based Practice at Bond University in Australia, the thesis framework for understanding the problem of overdiagnosis and its literature is the evidence-based approach to medicine. This approach explicitly involves a focus on rigorously discovering how well interventions work, for whom, and what harms they do, rather than relying on the opinions of experts.[10] A second key feature of the evidence-based approach is to summarise all the least-biased evidence, and then incorporate that evidence with clinical expertise and patient preferences and values in order to make more informed health care decisions.

While the phrase “evidence-based medicine” arose in the 1990s, the roots of the approach date back deep into the history of attempts to empirically evaluate the effects of medical interventions. In 1753 James Lind famously wrote up his controlled experiments testing six different treatments for scurvy, together with a systematic summary of what had previously

been published on the subject.[11] Through the 20th century the science of evaluation and research synthesis continued to develop,[12] and by the 1970s epidemiologist Archie Cochrane, among others, was persuasively arguing for what many believed, mistakenly, was already common practice: routine rigorous evaluation of medical interventions, and accessible systematic summaries of the resulting evidence.[13]

Another relevant milestone in the history of the evidence-based approach was the report from the 1979 Canadian Task Force on the Periodic Health Examination, which applied a then new, but now familiar system for rating the strength and quality of studies being summarised, using a hierarchy with randomised trials at the top and expert opinion at the bottom.[14] The value of expert opinion was further challenged by the presentation of a study at a landmark 1993 New York Academy of Sciences conference. The study by two leading advocates of the evidence-based approach, Andy Oxman and Gordon Guyatt, found review articles written by experts were generally of “inferior quality” and that “the greater the expertise the more likely the quality is to be poor.”[15] At the same 1993 conference the concept for the international Cochrane Collaboration was announced. Taking its name from Archie Cochrane, a new global not-for-profit organisation was launched, dedicated to producing accessible systematic reviews of the evidence for thousands of health care interventions.[16]

It is not coincidental that the increasingly rigorous conceptualisation and measurement of overdiagnosis taking place in recent decades - particularly but not exclusively in relation to cancer screening - has run somewhat in parallel with the rise of the evidence-based approach to medicine. As per the examples below, what started as informed theoretical speculation about possible harm, has grown in a number of cases into reliable evidence about the existence of overdiagnosis and estimates of how often it occurs - particularly in relation to cancer screening - through the accumulated results of observational studies, randomised controlled trials and systematic reviews of those studies.

The aim of this thesis is to contribute to our understanding about the problem of overdiagnosis, its nature, causes and consequences, and how we might start to prevent it. The literature review covers some key examples from the overdiagnosis research on cancer and non-cancer conditions, as flagged in Table 1, as well as key analysis of generic aspects of

the problem abstracted from overdiagnosis research on individual conditions. The review also explores related research on medicalisation, examines the issue of expanding disease definitions and closes by touching on research and debate about how guidelines may be contributing to the problem of medical excess.

Table 1. Examples covered in literature review

Examples covered in this review	Importance
<i>Cancers</i>	
Prostate and breast cancer screening	Examples show how speculation about potential for overdiagnosis as a risk of screening programmes has moved to convincing evidence and estimates of magnitude of the problem
Neuroblastoma screening	Historical example being increasingly cited in literature showing how tumours can regress, and treatment of indolent tumours can cause harm. Highlights need for caution about initial enthusiasm for interventions, rigorous evidence-based evaluation and analysis
<i>Risk-based conditions</i>	
High blood pressure High cholesterol Osteoporosis Overweight	Examples of changing definitions of risk-based conditions, and lowering diagnostic thresholds which label more and more people at lower risks of future illness, some of whom will receive a diagnosis and treatment that will do more harm than good
<i>Behavioural/mental disorders</i>	
Attention Deficit Hyperactivity Disorder	Example of a behaviour/symptom-based condition cited in overdiagnosis and medicalisation literature, where there is concern about expanding disease boundaries

A review of the literature

For more than 30 years the scientific literature has featured growing concern and evidence about “overdiagnosis”, both in relation to cancer and cancer screening, and non-cancer conditions. Much of the literature is analysis or commentary, but there are also many

primary research studies employing a wide range of methods, including but not limited to: autopsy studies which demonstrate important reservoirs of indolent disease, for example for prostate cancer and ductal carcinoma in situ; observational studies including studies analysing incidence and mortality trends; studies that review patient records to check the veracity of existing diagnoses and uncover overdiagnosis; randomised controlled trials of screening programmes; systematic reviews of studies; and ultimately inquiries or other official reports which review and summarise all the evidence including where relevant multiple systematic reviews. As evidence for overdiagnosis is better established in relation to cancer screening, I will address that literature first.

Prostate and breast cancer screening

By the 1980s cancer screening activities were coming under increasing scientific scrutiny, facing specific questions about the risk that programmes could cause the overdiagnosis of non-progressive cancers, at a time well before important randomised controlled trials of screening had reported. For example in 1985 Love identified “overdiagnosis or diagnosis of ‘pseudo-cancers’” as a potentially “major problem” with screening for prostate cancer.[17] Referring to screening using digital rectal examination, he pointed out that without randomised trial evidence it was impossible to know if early detection via screening improved prognosis, and that “interpreting the results of treatment for asymptomatic cases diagnosed by screening is difficult because ofpossible overdiagnosis of nonprogressive cancers.” Importantly Love’s 1985 article drew on evidence and analysis from the previous decade, including the 1979 report of the Canadian Task Force on the Periodic Health Examination,[14] highlighting the fact that awareness of the problem of unnecessary diagnoses, and concerns about the harms of screening pre-dated more common usage of the specific term “overdiagnosis”. Also in 1985 Chamberlain noted encouraging early evidence breast cancer screening could reduce cancer deaths, but speculated that mammography “may have the disadvantage of overdiagnosing cases of borderline non-invasive neoplasia which might not progress to invasive cancer within the woman's lifetime.”[18]

As large trials were initiated and reported and systematic reviews summarised the resulting evidence through the intervening three decades, these early speculations about prostate and breast cancer screening have proved prophetic. In response to mounting scientific evidence

and concern over benefits and harms of breast screening, in the United Kingdom an independent inquiry was recently initiated by Cancer Research UK and the national department of health. An independent panel lead by epidemiologist Sir Michael Marmot was commissioned to investigate the current state of the evidence. Following a review of all the accumulated evidence, and hearing testimony from experts, the report concluded in 2012 that along with screening benefits “the major harm of screening considered by the Panel was that of overdiagnosis”, defined as a cancer “diagnosed by screening that would not otherwise have come to attention in the woman’s lifetime.”[19]

The results of Marmot’s independent review, published simultaneously in *The Lancet*, estimated that 19% of the breast cancers diagnosed during the active mammography screening period are overdiagnosed cancers.[20] Reflecting on-going debate about the best ways to measure the occurrence of overdiagnosis, the authors stressed this was an estimate only, and included this important caveat: “Since the estimates provided are from studies with many limitations and whose relevance to present-day screening programmes can be questioned, they have substantial uncertainty and should be regarded only as an approximate guide.”[20] Complicating estimation of the magnitude of overdiagnosis resulting from screening programmes is a lack of research attention to the harms of screening, even in high quality evaluations. As Heleno and colleagues found, only a small fraction of randomised trials of cancer screening have quantified rates of false positives and overdiagnosis.[21]

Also in 2012, the influential United States Preventive Services Task Force handed down its evidence-based report on the accumulated evidence around prostate cancer screening, recommending against screening, and finding overdiagnosis to be a major potential harm of screening. The publicly funded independent Task Force concluded there was “convincing evidence that PSA-based [prostate-specific antigen] screening leads to substantial overdiagnosis of prostate tumors”, with estimates ranging from 17% to 50%.[22] While neither of these major reports is the last word on the magnitude of overdiagnosis for these screening activities, and debate about methods and the range of estimates continue,[23,24] they help mark a more formal official acceptance that the problem represents a significant public health challenge. Importantly, independent panels produced both of these landmark

reports. One initial implication of this evidence is the clear need to routinely inform people invited to undergo screening about the risk of overdiagnosis.

Neuroblastoma screening

One valuable case study which emerges from a long-term review of the overdiagnosis literature is screening for the potentially fatal childhood cancer called neuroblastoma. Because the presence of neuroblastoma could be detected with a urine test, there was great hope in some nations in the 1970s and 1980s that mass screening of young infants could identify and treat early neuroblastoma tumours, and prevent premature death. Again, as with prostate and breast cancer, looking back over the literature, we see increasingly rigorous evidence-based scrutiny of the risks and benefits of neuroblastoma screening programmes, and over time and with the accumulation of evidence and its critical appraisal, we see initial enthusiasm turn give way to doubt and finally concern that screening was doing more harm than good, chiefly because of overdiagnosis and subsequent overtreatment of benign tumours.

Extensive neuroblastoma screening programmes were set up in Japan in the 1970s, and by the early 1980s enthusiastic reports on the benefits of screening were appearing in the medical literature, inspiring screening programmes elsewhere around the world. In 1991 an epidemiological analysis of those earlier enthusiastic reports found “the data needed to definitively assess the value of screening were not a part of those reports and that the benefits claimed from the reported data could be due to overdiagnosis.”[25] Screening was certainly finding early tumours in infants, but it was unclear how many of those newly discovered tumours would have ever gone on to cause harm if they hadn’t been detected via screening. By 1994, another analysis of the existing literature on neuroblastoma screening was raising even more serious doubts.[26] While noting that many child cancer experts were still advocating for screening, according to the 1994 analysis of the data “screening is differentially picking up the tumours that are least likely to progress” and that screening “ ‘overdiagnoses’ many non-progressive cases, with consequent physical and psychological morbidity.” In other words many infants were undergoing invasive treatment unnecessarily. The paper concluded that “on balance present evidence suggests that the number of deaths that could be prevented by screening is small and the potential for overdiagnosis is great.”

By 1998 Ajiki and colleagues published research in *Cancer Causes and Control*, analysing the population-based cancer registry in Osaka in Japan, showing that the introduction of neuroblastoma screening corresponded with a massive increase in incidence of the disease, but with no corresponding change in the rate of death.[27] They found the “annual age-standardized incidence rate per million children increased from 7.5 in 1970-84 to 20.5 in 1985-94, while the mortality rates did not differ between these two periods.” The authors concluded “mass screening for neuroblastoma causes harm because of overdiagnosis, and it has little effect on decreasing the incidence and the mortality of neuroblastoma at 1-4 years of age.” Four years later, in 2002, a controlled study was published in the *New England Journal of Medicine*. [28] That study compared the outcomes for one and a half million children in German states who underwent screening, and over two million children in other states which didn’t have screening. Schilling and colleagues found “substantial” overdiagnosis of children diagnosed by screening – children who would not benefit from earlier diagnosis and treatment - and the authors concluded the evidence did not support the continuation of screening.

Neuroblastoma now appears in the overdiagnosis literature as a powerful example of the need to rigorously assess screening programmes for risk of overdiagnosis.[29-31] In the *Archives of Internal Medicine* Lauer has made the point, which has a much wider resonance across the literature on overdiagnosis, “while our diagnostic technologies were good enough to detect early disease, they were not able to distinguish between those tumors that represented a genuine threat to a child’s life and those that did not.”[30] And in *The Lancet Oncology* Esserman and colleagues have recently highlighted that much harm was done because a “spontaneously regressing type” of cancer, which had not been previously recognised, was detected and treated with surgery and chemotherapy: “This example draws attention to two important principles: tumours can regress, and treatment of indolent tumours can often cause harm.”[31]

Abstracting the problem from the examples

Alongside many papers in the literature that concern specific diseases, there are a small number which offer an analysis of the nature of overdiagnosis, largely with the focus on cancer screening, where evidence is strongest. While not the only institution in the world

offering this kind of analysis, much work stands out in this regard from the community of researchers based at the university at Dartmouth College in New England in the United States. Dartmouth has emerged as a highly influential centre bringing rigorous evidence-based scrutiny to both the benefits and harms of medical interventions, for understanding overdiagnosis, and communicating about the problem.

In 1993, clinician-researchers Black and Welch published an analysis article in the *New England Journal of Medicine*, showing how general advances in diagnostic imaging were causing overestimations of disease prevalence and therapy benefits.[32] The article drew on emerging evidence related to several cancers, including thyroid, prostate, lung and breast cancer and one non-cancer condition, abdominal aortic aneurysm. The article also cited an evaluation of screening dating back to 1969, which noted that screening would detect cases “which may never go on to clinically recognizable disease”.[33] The 1993 analysis showed how new technologies like CT scanning enabled detection of smaller and smaller “abnormalities”, often of uncertain prognosis, but which were nevertheless classified as disease and routinely treated. This, authors argued, was leading to overestimates of the prevalence of genuine disease and exaggerations of the effectiveness of treatments, as clinicians treated more and more “disease” that would never have caused harm if it remained undetected. This in turn was fuelling an increasingly intense cycle, where misplaced assumptions about the benefits of detecting and treating tinier abnormalities were driving more potentially unnecessary diagnosis and treatment, causing harm and waste.

The 1993 *New England Journal of Medicine* article did not use the term “overdiagnosis” but did describe “large reservoirs of clinically occult disease” and diagnosis and treatment that was conferring “little or no benefit”. Issuing a prescient warning the authors speculated that, “despite clinicians best intentions, many patients may have been labelled with diseases they do not really have, and many may have been given therapy they do not really need.” The article concluded with a range of recommendations, particularly for more precision in research and clinical practice about the exact size of “abnormalities” and more rigorous research on the risks and benefits of treating symptomless or subclinical problems.

Five years later in 1998, Black published a paper titled “Advances in radiology and the real versus apparent effects of early diagnosis”, drawing from and developing ideas in the 1993

paper, but this time explicitly using the term “overdiagnosis”.[34] Black’s article discussed a range of biases relevant to the science around early diagnosis, including the problem of *lead time* bias in survival statistics, often misused by advocates of screening programmes to inflate benefits. As he explained, even if having an early diagnosis has no effect on extending the time at which symptoms ultimately emerge for a person, or death from disease happens, it will appear as if survival has been prolonged, if survival is measured from time of diagnosis. Getting an early diagnosis in this scenario could simply mean living with the diagnosis for longer, with no real benefit in terms of reducing suffering or extending life. *Length* bias pertains to comparisons “not adjusted for the rate of disease progression.” An awkward fact of screening is that it tends to more often detect disease which is slower growing and may never cause harm, rather than rapidly progressive disease.

Changing disease definitions

In 1999, another Dartmouth team, Schwartz and Woloshin, examined the issue of early diagnosis of disease from another perspective - the way in which disease definitions were expanding, catching more people at lower risk of actual illness.[35] They chose four well known “conditions” - high blood pressure, diabetes type 2, high cholesterol and being overweight - where professional societies had recently proposed lowered diagnostic thresholds. They showed how the changes would dramatically increase the number of Americans labelled as having these conditions to almost 75% of the total adult population of the United States. The authors outlined several reasons for concern including: limited evidence that the newly described “patients” would benefit from treatment; the risk of drawing resources and attention from those with more serious conditions; and the harms of diagnosis and treatment for those who don’t benefit. Echoing alarm about the beguiling yet dangerous cycle of increasing intensity, as in the discussion above, they pointed out that “lower diagnostic thresholds will not only raise the prevalence of disease, they will appear to improve disease outcomes.” Because milder cases would now be included in population statistics on prevalence, the “average” blood pressure or blood sugar levels of all those labelled would appear to be improved, and treatments, now targeted at less severe cases, will appear to work more effectively.

In Europe around this time, Getz and colleagues were conducting similar research and raising related concerns, arguing that the issue of lowering diagnostic thresholds demanded much more critical scrutiny and may ultimately be causing more harm than good to many people.[36] Applying diagnostic thresholds embedded in professional society guidelines for high blood pressure and high cholesterol to over 60 000 Norwegians aged 20-79, Getz and colleagues found 76% of people had “unfavourable” risk profiles, despite Norway having one of the world’s longest living and healthiest populations. They found by age 24, 50% of people had blood pressure or cholesterol levels above recommended cut-off points, by age 50, the figure was 90%. The authors explored ethical dilemmas around labelling and medicalising so many among the healthy population, and pointed to resulting problems of health system sustainability. Importantly they pointed to evidence that giving people information about risk of future disease “can cast shadows of doubt and insecurity over people’s lives”, which could potentially “undermine an individual’s subjective experience of integrity, well-being and health.”

Growing evidence, growing recognition

By 2010 Black and Welch published what would become one of the most highly cited articles within the overdiagnosis literature. It was titled “Overdiagnosis in Cancer” and was published in the journal of the National Cancer Institute, *JNCI*. [29] The authors described how sometimes large reservoirs of indolent cancer - as evidenced by autopsy studies - were being uncovered by screening programmes targeting the healthy. This was then causing significant overdiagnosis, as demonstrated by both randomised controlled trials of screening programmes, and observational studies analysing big increases in disease incidence unaccompanied by increases in rates of premature death. Where data from randomised trials were available, Black and Welch offered worrying estimates of the magnitude of cancer overdiagnosis: about 25% of mammographically detected breast cancers; 50% of x-ray or sputum-detected lung cancers; and 60% of prostate-specific antigen detected prostate cancers. The article also articulated the complex “trade-off” for people making decisions about screening, “between the potential to avert a cancer death and the risk of overdiagnosis”. In conclusion the authors offered a range of suggestions for addressing the problem: more research on numerical estimates of overdiagnosis risk and patient

preferences; more information and education; and consideration of raising thresholds at which diagnoses are made.

In 2011 the critically acclaimed book *Overdiagnosis: making people sick in the pursuit of health* was published.[1] Authored by Welch, Schwartz and Woloshin, the book offered an accessible summary of the problem for overdiagnosis, meticulously citing a range of evidence to challenge the pervasive myth that an early detection approach is always the best policy. Examples of conditions where overdiagnosis was a potential harm for people covered both cancers and non-cancers. The non-cancer examples included several risk-based conditions where diagnostic thresholds have been lowered in recent decades - e.g. high cholesterol and low bone mineral density - as well as other conditions where diagnostic technology is enabling smaller and smaller potentially harmless “abnormalities” to be diagnosed - e.g. abdominal aortic aneurysm and pulmonary embolism. In each case, people at lower risks for health problems have become at higher risk of being overdiagnosed: given medical labels and treatments that might do them more harm than good. Determining the exact magnitude of those risks however remains challenging.

Challenges in quantifying risk of overdiagnosis on non-cancer conditions

The review of the literature conducted for this thesis demonstrates clearly that quantifying the risk of overdiagnosis for any given condition is highly complex and uncertain. While numerical estimates have emerged in recent years in relation to some cancer screening programmes, they are still commonly surrounded by wide confidence intervals of uncertainty, and on-going debate about methods.[37] Methods for quantifying the risks of overdiagnosis with non-cancer conditions are generally less well-developed, and made more complicated by uncertainty and controversy around the definitions of many conditions, and the thresholds or cut-points at which they are diagnosed. This is particularly the case when dealing with the wide range of common “conditions” which are essentially risk factors for future illness - including for example high blood pressure, high cholesterol, osteoporosis, and even diabetes type 2 - conditions which are diagnosed and treated using surrogate endpoints or biomarkers, where the focus is on numbers rather than the person’s symptoms.

As part of broader concern about the risks of overdiagnosis and overtreatment, the importance and value of surrogates is under increasing scrutiny,[38] and the still well-

established practice of diagnosing numerical risks as diseases is being challenged.[38] In 2010 the United States Institute of Medicine, IOM, released a major report on biomarkers and surrogates.[40] While stressing their utility, the report raised many serious questions about how they were being used in medical practice. The report warned against a generalised over-reliance on intermediate end-points rather than clinically meaningful outcomes, and called for much more rigorous evaluation of how surrogates are used. In 2011, Ioannidis and Panagiotou found the importance of biomarkers tended to be overestimated in highly cited studies - often early enthusiastic reports - as compared to subsequent meta-analyses.[41] Editorialising about that study in *JAMA*, Bossuyt outlined the hope that biomarkers could help deliver a more “personalised medicine” - better locating those people at risk of future illness, detecting early disease, and identifying those most likely to benefit from treatment - but argued “most of these promises have yet to be fulfilled”. [42] Earlier, in an article entitled “Against Diagnosis”, Vickers and colleagues had advocated a dramatic shift away from diagnosing risk-based conditions in medicine, and urged a move towards risk-prediction rather than diagnostic approaches.[39] With such controversy and uncertainty over what constitutes a “condition” and whether to even diagnose it, attempts to identify where appropriate diagnosis ends and overdiagnosis begins is extremely challenging.

As with cancer, studies in non-cancer conditions appearing in the literature have employed a variety of methods, sometimes enabling researchers to make tentative estimates of the magnitude of overdiagnosis. For example in Denmark in 2013 researchers retrospectively reviewed the patient records of almost 900 people under the age of 65 diagnosed with dementia, finding only 60% met the diagnostic criteria.[43] In Tanzania, researchers prospectively observed the treatment and outcomes for over 4000 people diagnosed with severe malaria across 10 hospitals, finding almost half did not have malaria.[44] Writing in *The BMJ* in 2004 authors concluded “malaria is commonly overdiagnosed in people presenting with severe febrile illness” and that this is associated with “a failure to treat alternative causes of severe infection”, though others will see this as an example of misdiagnosis, rather than overdiagnosis. Other studies analyse population statistics finding big increases in incidence but little change in mortality trends over time, as has occurred

with research suggesting widespread overdiagnosis and overtreatment of pulmonary embolism.[4]

While many studies in the literature find evidence of overdiagnosis, others do not. In one example Pohl and Welch documented a rapid rise in incidence of esophageal adenocarcinoma between 1975 and 2001, but because there was little change in the proportion of people found with in situ or localized disease at diagnosis, and because that rise was accompanied by a similar rise in mortality, overdiagnosis was excluded as an explanation for the increasing incidence.[45] In this case researchers concluded there was a genuine increase in disease burden. In another example a review of the literature on Attention Deficit Hyperactivity Disorder, ADHD, found the criteria for diagnosing the condition had broadened, but little evidence of widespread overdiagnosis.[46]

Estimating the nature and magnitude of overdiagnosis is made more complicated because different types of conditions are vulnerable to different drivers of potential excess. For the risk-based conditions, exemplified by high blood pressure, expert panels changing diagnostic cut-points on the basis of new trial evidence is a key driver of expansion in the patient pool. For physical but often asymptomatic conditions, exemplified by what has happened with the expansion in diagnosis of pulmonary embolism, a key driver has been a change in diagnostic technology: the advent of the CT scan which enables the identification, diagnosis and treatment of much smaller clots, many of which are likely to have a benign prognosis if left undetected.[4] For mental disorders, where there is often controversy over the appropriate boundary between the condition and normal life experience, a different set of factors, including changes in diagnostic thresholds, are driving expansions in the patient pool.

Medicalisation

Many papers in the overdiagnosis literature discuss mental disorders, dating back almost 40 years to an article in 1978 examining the methodological difficulties facing epidemiological studies of what were then described as affective disorders, including bipolar disorder and depression.[47] Prefiguring much contemporary debate, Turns concluded that the label of “affective disorders” covered conditions of varying severity, that the most prevalent conditions had a “high rate of spontaneous recovery”, and that “mental health professionals

may, in fact, be overdiagnosing and overtreating”.[47] This debate about potential overdiagnosis of mental health disorders is perhaps best exemplified by debate around ADHD, which has also been used as an example in the related sociological literature on medicalisation.

For more than four decades the leading medical sociologist Peter Conrad has been describing the process of medicalisation - widening medical boundaries - sometimes using ADHD as an example of broader trends. In 1975 Conrad described the medicalisation of deviant behaviour and medicine’s role in social control, using the example of “hyperkinesis”, a medical label for a suite of behaviours in children that would later be described as ADHD.[48] In 2000 Conrad published an article on the expansion of medical categories, this time using the example of the way criteria for ADHD were widening from children to include adults as well, and showing how lay people, lay-professional alliances and the media were all playing a role in this dramatic expansion.[49] “In the adult ADHD case the diagnosis is embraced and promoted by the people who receive it” wrote Conrad and Potter. “In this case, medication treatment may be seen as much as an enhancement as a form of social control.” In 2005, in an article titled “The Shifting Engines of Medicalization” Conrad described the rising influence of consumers, insurers and the biotechnology and the pharmaceutical industries, arguing that “medicalization is now more driven by commercial and market interests than by professional claims-makers”.[50] In light of this shift to the market place, the article also called for sociologists of medicine to more often consider political economy perspectives. Most recently in 2014, the sociologist described a coming “globalization of ADHD”, showing how the North American medical label was migrating to many nations, carried by a range of vehicles including global pharmaceutical companies, western psychiatry, highly accessible internet-based screening checklists and well-organised advocacy groups.[51]

Others have described a move from what was previously understood as medicalisation to a more all-encompassing “biomedicalization”, occurring as a result of vast economic, political and social changes, from the transformation of the economy to changes in personal identify which are emerging from the interconnected rise of biomedicine and information technologies.[6] “In the biomedicalization era” wrote sociologists Clarke and colleagues in a

landmark 2003 article, “what is perhaps most radical is the biomedicalization of health itself”, an era when “it is no longer necessary to manifest symptoms to be considered ill or ‘at risk’”. Similarly Armstrong has detailed the inexorable rise of what he calls “surveillance medicine”, which through the latter part of the 20th century reconstructed the nature of disease, to become “less the illness per se but rather the semi-pathological pre-illness at-risk state.”[52]

A small literature also relevant to discussions of overdiagnosis addresses the problem known as “disease-mongering”, a phrase popularised by Payer,[53] but with an important debt to Illich’s influential work on the medicalisation of life.[5] Disease-mongering, also described as “selling sickness”,[54] is the process of portraying more and more ordinary life as the signs and symptoms of severe and treatable diseases and disorders, commonly motivated by a desire to build markets for those who sell or deliver treatments, and often driven explicitly by pharmaceutical industry funded “disease awareness” campaigns run in alliance with industry-linked health professionals and advocacy groups. A special collection of articles on disease-mongering was published in the open access journal *PLOS Medicine* in 2006, [55] covering conditions including bipolar disorder,[56] erectile dysfunction,[57] female sexual dysfunction,[58] and restless legs syndrome.[59] The paper on restless legs syndrome from Dartmouth authors Woloshin and Schwartz analysed how pharmaceutical marketing helped to distort media coverage and blur the lines between common difficulties and a treatable syndrome. “The news coverage of restless legs syndrome is disturbing” they wrote. “It exaggerated the prevalence of disease and the need for treatment, and failed to consider the problems of overdiagnosis.”

While overdiagnosis can lead to overtreatment - for example if someone was unnecessarily diagnosed with restless legs syndrome and then treated for it - problems of overuse more generally can also be unrelated to overdiagnosis, and driven by some different factors.

While sitting under the wider umbrella of “too much medicine”,[60] the broad and extensive literature on waste and overuse [7, 61]- whether CT scans of children,[62] inappropriate polypharmacy among the elderly,[63] or poorly evaluated procedures like vertebroplasty[64] - is largely outside the scope of this thesis.

Guidelines, Evidence and Overdiagnosis

A final part of the scientific literature relevant to this thesis pertains to clinical guidelines. While guidelines have been promoted as the way high quality evidence can be translated into clinical practice and produce improved patient care, there is increasing evidence and concern about flaws in both the way guidelines are produced and the constitution of panels which produce them, as well as their potential to drive overdiagnosis and overtreatment. In a 2012 review of 130 randomly selected guidelines,[65] Kung and colleagues found generally poor compliance with IOM standards for developing and reporting guidelines.[66] In relation to the composition of panels producing guidelines, Kung and colleagues found that independent “information scientists” and patient or public representatives were rarely included on panels, and that where financial conflicts of interest were reported, they were pervasive, including among panel chairs. A 2011 systematic review of studies of guidelines and financial ties similarly found conflicts of interest among clinical guideline panels were extremely common.[67]

While no studies have systematically investigated links between guideline output and overdiagnosis, there is significant anecdotal concern about the connection. The former head of the task force which compiled the fourth edition of the influential *Diagnostic and Statistical Manual of Mental Disorders*, the *DSM IV*, psychiatrist Allen Frances, has expressed public concern that the *DSM IV* has unwittingly contributed to an explosion of unnecessary diagnoses in the areas of attention deficit, autism, and bipolar disorder.[68] Taking a broader interest in guidelines and disease definitions, Frances has raised doubts about many contemporary guidelines, observing that they are generally developed by experts with intellectual or financial conflicts that “biases them toward overdiagnosis and overtreatment.”[69] Former president of the Royal College of General Practitioners in the United Kingdom, Iona Heath, has gone further: “Whenever I see the sort of guidelines that are, right now, driving overdiagnosis and overtreatment, I think of this: our responsibility not to follow the rules.”[70]

Part of the concern is about the proliferation of single-condition guidelines, and their distorted impact on the way care is delivered and the way quality of care is measured. In *The BMJ* in 2009 Heath and colleagues raised questions about the appropriateness of applying

narrow disease-specific specialist guidelines to the complexity of primary care, where people present with multiple co-morbidities and complex physical, psychological and social problems, and then measuring the quality of patient care based on the application of such narrow guidelines.[71] Similarly, in a provocative article in 2012 in *The BMJ*, titled *Beyond Diagnosis*, primary care clinician and researcher Mangin and colleagues pointed to the weakness of the single-condition evidence embedded in evidence-based guidelines, and called for a shift from thinking about individual abstract diagnoses, to thinking more holistically about the care of real people. Such a shift is necessary, the authors argued, in order to provide good care to people with multiple co-morbidities, and in particular to avoid poly-pharmacy that may result from adherence to multiple single-condition guidelines and their related quality measures.[72]

The work of Heath, Mangin and others has helped expose the unintended consequences of the rise and rise of the evidence-based approach to medicine, a problem outlined in a 2014 article by Greenhalgh and colleagues, titled “Evidence based medicine: a movement in crisis?”[73] Ironically the application of the evidence-based approach is increasingly revealing how “evidence” can be routinely distorted and even corrupted by vested interests both financial and professional, how an unmanageable proliferation of single condition “evidence-based” guidelines can cause overtreatment, and how “evidence” is increasingly harnessed to detect and intervene in “non-disease”, producing the real risk of overdiagnosis.[73] At the same time the systematic review methodology at the heart of the evidence-based approach has increasingly gained access to unpublished data, exposing the limited benefits and previously hidden harms of many common “evidence-based” interventions, a recent example being findings about widely used influenza treatments.[74] The broad movement behind the evidence-based approach appears to have entered something of a crisis and there are currently discussions of a possible renaissance, as I explore when discussing responses to the problem of overdiagnosis in chapter 8.

Aims, research questions and subsequent chapters

Following the initial scoping of the literature and the planning for the thesis, several areas of research interest emerged. In a broad sense, more work on the basic nature of the problem

was clearly required. While evidence about the risk of overdiagnosis was most mature in relation to cancer screening, more research was required on how and why disease definitions were expanding, and how those changes were helping drive the problem of overdiagnosis. Another gap in the literature was data on public knowledge and perceptions about overdiagnosis. And finally, a clear need existed to imagine, design and evaluate a range of potential responses to the problem, and to articulate how medical evidence, and its synthesis and use in guidelines, might be better marshalled to prevent rather than exacerbate overdiagnosis.

In summary, the broad aims of the thesis were to answer the following research questions:

1. What is overdiagnosis and what is driving it?
2. Who is defining diseases and with what financial ties to industry?
3. How and why are disease-definitions expanding?
4. Awareness and views about overdiagnosis among the public: are people being informed about the overdiagnosis risk of screening and what does the public think about conflicted guideline panels which change disease definitions?
5. How might “evidence” be produced and used in ways that better respond to the problem of overdiagnosis?

The first aim of the thesis, arising from the scoping of the literature, was to produce an accessible overview article describing overdiagnosis, its drivers and possible responses, to help introduce the topic to a wider group of health professionals, policy-makers and the public. Chapter 2, published as a peer-reviewed paper in *The BMJ* in 2012 is the result of that initial scoping of the literature.[9] The paper uses a range of brief examples of cancer and non-cancer conditions where overdiagnosis has been identified as a risk, to help illustrate the problem. Since publication in 2012 the article has been well-cited in the scientific literature and helped bring public attention to the problem, through high profile domestic and global media coverage.[75, 76] The paper also introduced two important and related projects initiated as part of my work on overdiagnosis through the development of this thesis.

Arising from the discussions with colleagues at the inception of the thesis, and reinforced by the initial scoping of the overdiagnosis literature, it became clear it was time for an international multi-disciplinary scientific conference on overdiagnosis, to share the emerging science, bring researchers together and advance research and policy agendas. A small planning meeting took place in 2012, from which a global alliance of academic, journal and consumer partners emerged, to hold what has become a series of highly successful international scientific conferences called *Preventing Overdiagnosis*.^[77] The first meeting took place in 2013 at Dartmouth, the second in 2014 at the University of Oxford, and the third is scheduled for September 2015 at the National Cancer Institute in the United States. The second project foreshadowed in the paper was the launch of a new series of peer-reviewed articles in *The BMJ*,^[60] documenting, condition by condition, the problem of expanding disease definitions and risk of overdiagnosis.

While there has a strong focus on cancer screening in the overdiagnosis literature, a key focus of the thesis is investigating the problem of expanding disease definitions, and how it might relate to the problem of overdiagnosis. While the literature had included several papers discussing different condition-specific examples, no study had systematically examined the expert guideline panels which review and change the definitions of common conditions. Chapter 3 is a peer-reviewed paper featuring the results of a major study of expert panels which review and change disease definitions, published in *PLOS Medicine* in 2013.^[78] Our study made valuable findings about the extent to which definitions are being expanded, the way they are being expanded, whether the risks of such expansion - including overdiagnosis - were being investigated, and the extent to which expert guideline panel members have financial ties to companies with an interest in the size of disease markets.

To investigate more deeply how and why disease definitions are changing, the thesis used a case study involving a widened disease definition which was the subject of much scientific controversy. Chapter 4 is the result of investigating the case study of chronic kidney disease, CKD, which was published as a peer-reviewed article in *The BMJ* in 2013.^[79] This chapter is a result of research into the controversy over the definition CKD, which labels around half of

all those over the age of 70 as diseased. Closely analysing a decade of literature from proponents and critics of the CKD definition, the chapter brings important insights into the way controversial decisions are promulgated and defended in the face of sustained scientific criticism. The chapter urges caution in applying the controversial CKD definition's diagnostic thresholds and concludes the definition is so problematic that an independent review by an un-conflicted panel is required.

As covered above in the review of the overdiagnosis literature, while there are varying and uncertain numerical estimates of magnitude, it has become clear that overdiagnosis is a genuine risk of some cancer screening activities, with evidence being well-established for breast and prostate cancer. However, there has been little investigation into how often people invited to screening are being informed about the risks. More broadly there are very few survey data in the literature about public awareness of and attitudes about overdiagnosis. As part of the thesis, with research colleagues and staff from a social research company experienced in health surveys, we designed and piloted a new questionnaire and ran a national community survey of 500 adult Australians investigating understanding of and attitudes about overdiagnosis. The results appear in the submitted manuscript that is chapter 5 of the thesis.[80] Drawing from the results of my study of expert guideline panels covered in chapter 3, as part of the survey questionnaire, we included questions about attitudes to expert panels with financial ties.

Chapter 6, a submitted manuscript, features the results of a qualitative analysis of public responses to our survey question "What do you think the term overdiagnosis means?".[81] While growing evidence has brought recognition of the need to start communicating with people more effectively about the risk of overdiagnosis, there was no survey data on what the general community understands the term overdiagnosis to mean. At a time when there is on-going scientific debate about how best to define overdiagnosis, and its relationships with overuse and the wider problem of too much medicine, our survey asked 500 Australians what they understood the term overdiagnosis to mean. The results, and our thematic analysis of responses, start to bring the voice of the community into the debate about overdiagnosis, and offer a rich data set for those designing communication strategies about overdiagnosis.

Possible responses to the problem of overdiagnosis are covered in chapters 7 and 8.

Published as a peer-reviewed article in *PLOS Medicine* in 2014,[82] chapter 7 explores how evidence can be used more effectively to combat overdiagnosis and related overtreatment.

The article looks at how the running of primary studies of tests and treatments, the production of systematic reviews and the reviewing and changing of disease definitions might all much more routinely include an explicit awareness of the risk of overdiagnosis. A key aim is to develop a more extensive evidence base on which to build disease definitions and diagnostic thresholds which reduce the risks of overdiagnosis and overtreatment, and which can be employed to better inform shared decision-making when there is controversy or uncertainty. These issues become part of a wider discussion in chapter 8 of the thesis findings and research and policy implications.

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Chapter 2 Preventing Overdiagnosis: how to stop harming the healthy

***BMJ* 2012;344:e3502**

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Medicine's much hailed ability to help the sick is fast being challenged by its propensity to harm the healthy. A burgeoning scientific literature is fuelling public concerns that too many people are being overdosed,[1] overtreated,[2]and overdiagnosed.[3] Screening programmes are detecting early cancers that will never cause symptoms or death,[4] sensitive diagnostic technologies identify "abnormalities" so tiny they will remain benign,[5] while widening disease definitions mean people at ever lower risks receive permanent medical labels and lifelong treatments that will fail to benefit many of them.[3,6] With estimates that more than \$200bn (£128bn; €160bn) may be wasted on unnecessary treatment every year in the United States,[7] the cumulative burden from overdiagnosis poses a significant threat to human health.

Narrowly defined, overdiagnosis occurs when people without symptoms are diagnosed with a disease that ultimately will not cause them to experience symptoms or early death.[3] More broadly defined, overdiagnosis refers to the related problems of overmedicalisation and subsequent overtreatment, diagnosis creep, shifting thresholds, and disease mongering, all processes helping to reclassify healthy people with mild problems or at low risk as sick.[8]

The downsides of overdiagnosis include the negative effects of unnecessary labelling, the harms of unneeded tests and therapies, and the opportunity cost of wasted resources that could be better used to treat or prevent genuine illness. The challenge is to articulate the nature and extent of the problem more widely, identify the patterns and drivers, and develop a suite of responses from the clinical to the cultural.

At the clinical level, a key aim is to better discriminate between benign "abnormalities" and those that will go on to cause harm. In terms of education and raising awareness among both the public and professionals, more honest information is needed about the risk of overdiagnosis, particularly related to screening. More deeply, mounting evidence that we're harming healthy people may force a questioning of our faith in ever-earlier detection, a renewal of the process of disease definition, and a fundamental shift in the systemic incentives driving dangerous excess.

Next year, an international scientific conference called Preventing Overdiagnosis aims to deepen understanding and awareness of the problem and its prevention. The conference will take place on 10-12 September 2013 in the United States, hosted by the Dartmouth Institute for Health Policy and Clinical Practice in partnership with *The BMJ*, the leading US consumer organisation Consumer Reports, and Bond University. The conference is timely, as growing concern about overdiagnosis is giving way to concerted action. The *Archives of Internal Medicine's* feature "Less is More" now regularly augments the evidence base,[9] high level health policy groups in Europe are debating ways to tackle excess,[10] and the recently launched Choosing Wisely campaign warns about dozens of potentially unnecessary tests and treatments across nine specialties.[11]

Many factors—including the best of intentions—are driving overdiagnosis, but a key contributor is advances in technology. The literature suggests several broad and related pathways to overdiagnosis: screening detected overdiagnosis in people without symptoms; overdiagnosis resulting from use of increasingly sensitive tests in those with symptoms; overdiagnosis made incidentally—"incidentalomas"; and overdiagnosis resulting from excessively widened disease definitions. These different pathways are not mutually exclusive, and a more rigorous classification of the different forms of overdiagnosis will be a focus of discussion at the 2013 scientific conference.

Screening detected overdiagnosis

This pathway to overdiagnosis occurs when a screening programme detects disease in a person without symptoms but the disease is in a form that will never cause that person symptoms or early death. Sometimes this form of disease is called pseudodisease. Contrary to popular notions that cancers are universally harmful and ultimately fatal, some cancers can regress, fail to progress, or grow so slowly that they will not cause harm before the individual dies from other causes.[5] As we will discuss below, there is now strong evidence from randomised trials and other studies comparing screened and unscreened populations that an important proportion of the cancer detected through some popular screening programmes may be pseudodisease.[4,12] Evidence from autopsy studies suggests a large reservoir of subclinical disease in the general population, including prostate, breast, and thyroid cancer, the bulk of which will never harm.[12] Similarly, screening the hearts of

people without symptoms or at low risk may also lead to overdiagnosis of coronary atherosclerosis and subsequent unnecessary interventions.[13] Our understanding of the nature and extent of overdiagnosis and the amount of pseudodisease detected by screening remains limited but is evolving, and as Woolfe and Harris observed recently in *JAMA*, “concern about overdiagnosis is justified.”[14]

Increasingly sensitive tests

People presenting to doctors with symptoms can also be overdiagnosed because changes in diagnostic technologies or methods have enabled the identification of less severe forms of diseases or disorders. It is becoming clearer that a substantial proportion of these earlier “abnormalities” will never progress, raising awkward questions about exactly when to use diagnostic labels and therapeutic approaches traditionally deployed against much more serious forms of disease.

Incidentalomas

Diagnostic scanning of the abdomen, pelvis, chest, head, and neck can reveal “incidental findings” in up to 40% of individuals being tested for other reasons.[15] Some of these are tumours, and most of these “incidentalomas” are benign. A very small number of people will benefit from early detection of an incidental malignant tumour, while others will suffer the anxiety and adverse effects of further investigation and treatment of an “abnormality” that would never have harmed them. As others have shown, the rapidly rising incidence for some cancers, set against relatively stable death rates, is a phenomenon suggestive of widespread overdiagnosis, whether from screening or the detection of incidentalomas.[12]

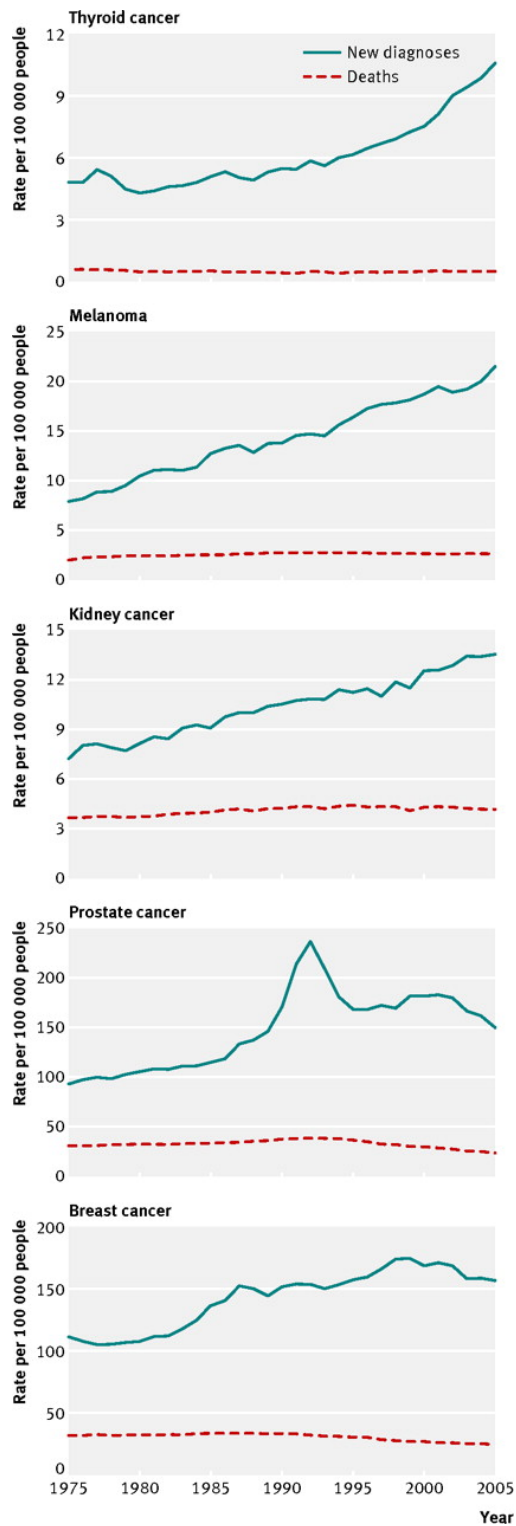
Excessively widened definitions

Another pathway to overdiagnosis is through disease boundaries being widened and treatment thresholds lowered to a point where a medical label and subsequent therapy may cause people more harm than good. Changing diagnostic criteria for many conditions are routinely increasing the numbers of people defined as sick,[16] causing virtually the entire older adult population to be classified as having at least one chronic condition.[17] This widening has happened both with asymptomatic conditions that carry a risk of an adverse event, such as osteoporosis, where treatments may do more harm than good for those at very low risk of fracture,[18] and for behavioural conditions such as female sexual dysfunction, where common difficulties have been reclassified as dysfunctions.[19]

Such changes in diagnostic criteria are commonly made by panels of health professionals with financial ties to companies that benefit directly from any expansion of the patient pool.[20] As definitions broaden and thresholds fall, people with smaller risks or milder problems are labelled, which means the potential benefits of treatment decline, raising the possibility that harms will outweigh benefits. As Welch and colleagues estimated in their 2011 book *Overdiagnosed*,[3] many people diagnosed and treated long term for near-normal cholesterol concentration or near-normal osteoporosis may be “overdiagnosed,” in the sense that they would never have experienced the events their treatments are designed to prevent.

Figure 1. Rates of new diagnosis and death for five types of cancer in the US, 1975-2005.

Adapted from Welch and Black, with permission.[12]



A related form of overdiagnosis occurs when people are diagnosed outside of already widened diagnostic criteria, as can occur when inappropriate manufacturers' norms exaggerate the incidence of abnormality,[21] when diagnostic methods wrongly label random or normal fluctuations in biomarkers as true abnormalities,[22] or when important qualifiers are left out of the process of diagnosis.[23]

Examples of overdiagnosis

The growing evidence on overdiagnosis suggests the problem may exist to varying extents across many conditions, including those for which underdiagnosis may simultaneously be a feature. For some conditions, the evidence remains tentative and speculative, for others it has become much more robust.

Breast cancer

Arguably the strongest evidence of overdiagnosis comes from studies of screening detected breast cancers, though estimates of its extent are wide ranging. A 2007 systematic review in *Lancet Oncology* found the proportion of overdiagnosis of invasive breast cancer among women in their 50s ranged from 1.7% to 54%.[24] An Australian study estimated the rate was at least 30%,[25] while a Norwegian study calculated 15-25%.[26] A 2009 systematic review in *The BMJ* concluded up to one third of all screening detected cancers may be overdiagnosed.[4] However, even with strong evidence from population based studies, it is currently impossible to discriminate between cancers that will harm and those that will not.

Thyroid cancer

While the chances of tests detecting a thyroid "abnormality" are high, the risk it will ever cause harm is low.[3,27] Analysis of rising incidence shows many of the newly diagnosed thyroid cancers are the smaller and less aggressive forms not requiring treatment,[28] which itself carries the risk of damaged nerves and long term medication.[3]

Gestational diabetes

A 2010 revision of the criteria defining gestational diabetes recommended a dramatic lowering of the diagnostic threshold, more than doubling the number of pregnant woman classified to almost 18%.[29] Proponents argue universal screening with the new definition will reduce health problems, including babies being "large for gestational age." [29] Critics, however, are calling for an urgent debate before the new expanded definition is more

widely adopted, because they fear many women may be overmedicalised and overdiagnosed, that the screening test has poor reproducibility for mild cases, the evidence of benefit for the newly diagnosed pregnant women is weak, and the benefit modest at best.[30, 31]

Chronic kidney disease

More than 10% of adults in the United States are now classified as having some form of chronic kidney disease.[32] A working definition launched as part of new clinical guidelines[33] asserts that an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m² and sustained for three months or longer is deemed abnormal, a decision critics argue automatically creates the potential for overdiagnosis, particularly among elderly people.[34]

According to Winearls and Glasscock in an article last year the new classification system is “like a fishing trawler” and “captures many more innocent subjects than it should.”[23] They estimate that up to one third of people over 65 may meet the new criteria, yet of these, fewer than 1 in 1000 will develop end stage renal disease each year. They also point to major problems with the reliability and consistency of the eGFR test and express concern many older people are being labelled on the basis of a single and potentially inaccurate laboratory measure. Elsewhere they have argued that “the majority of those held to have CKD [chronic kidney disease] have no identifiable kidney disease” and they’ve highlighted attempts by some organisations to move away from the controversial new definition, raise the threshold for diagnosis, and dramatically reduce prevalence.[35] Responding to criticisms, proponents have defended the new definition as being “clear, simple, and useful.”[36]

Asthma

Although asthma can be severe and may be underdiagnosed and undertreated, some studies suggest that there may also be substantial overdiagnosis. One large study in 2008 found that almost 30% of people diagnosed as having asthma did not have the condition, and almost 66% of those did not need drugs or asthma care during six months of follow-up.[37] The authors concluded, “A substantial proportion of people . . . may be overdiagnosed with asthma and may be prescribed asthma medications unnecessarily.” In the same year a Dutch study

found that of 1100 patients using inhaled corticosteroids, 30% may have been using the drugs without any clear indications.[38]

Pulmonary embolism

Doctors think of pulmonary embolism as a “not to be missed” diagnosis, because failure to detect it can have catastrophic consequences. Historically it was diagnosed only when the blockage was large enough to cause infarction of part of the lung or haemodynamic instability. In such patients, treatment with an anticoagulant or a thrombolytic agent was considered mandatory. Now, however, computed tomography (CT) pulmonary angiography can detect smaller clots, and there is uncertainty about whether treatment is always necessary.[39] Analysing trends before and after the widespread introduction of CT pulmonary angiography, Weiner and colleagues suggested that the almost doubling in incidence “reflects an epidemic of diagnostic testing that has created overdiagnosis,” with much of the increase consisting of “clinically unimportant” cases that “would not have been fatal even if left undiagnosed and untreated.”[40] An observational study is investigating the safety of not treating people with very small blood clots.[41]

Attention deficit hyperactivity disorder

Much has been written about expanding diagnostic definitions within mental illness and concerns about the dangers of overtreatment.[42] Debate has intensified with suggestions that current processes for defining disease may be contributing to the widespread overdiagnosis of conditions such as bipolar, autistic disorder, and attention deficit hyperactivity disorders.[43,44] One focus of concern is the possible overdiagnosis of children, who have no say in the appropriateness of a label that can permanently change their lives. This is particularly salient with attention deficit hyperactivity disorder.[45] A recent study of almost a million Canadian children found boys born in December (typically the youngest in their year) had a 30% higher chance of diagnosis and 40% higher chance of receiving medication than those born in January, with the authors concluding their findings “raise concerns about the potential harms of overdiagnosis and overprescribing.”[46]

Drivers of overdiagnosis

The forces driving overdiagnosis are embedded deep within the culture of medicine and wider society, underscoring the challenges facing any attempt to combat them (box 1). A key driver is technological change itself. As Black described in 1998, the ability to detect smaller

abnormalities axiomatically tends to increase the prevalence of any given disease.[5] In turn this leads to overestimation of the benefits of therapies, as milder forms of the disease are treated and improvements in health are wrongly ascribed to treatment success, creating a “false feedback” loop fuelling a “cycle of increasing testing and treatment, which may eventually cause more harm than benefit.”[5]

Box 1. Drivers of overdiagnosis

Technological changes detecting ever smaller “abnormalities”

Commercial and professional vested interests

Conflicted panels producing expanded disease definitions and writing guidelines

Legal incentives that punish underdiagnosis but not overdiagnosis

Health system incentives favouring more tests and treatments

Cultural beliefs that more is better; faith in early detection unmodified by its risks

The industries that benefit from expanded markets for tests and treatments hold wide reaching influence within the medical profession and wider society, through financial ties with professional and patient groups and funding of direct-to-consumer advertising, research foundations, disease awareness campaigns, and medical education.[8] Most importantly, the members of panels that write disease definitions or treatment thresholds often have financial ties to companies that stand to gain from expanded markets.[20] Similarly, health professionals and their associations may have an interest in maximising the patient pool within their specialty, and self-referrals by clinicians to diagnostic or therapeutic technologies in which they have a commercial interest may also drive unnecessary diagnosis.

Avoidance of litigation and the psychology of regret is another obvious driver as professionals can be punished for missing the early signs of disease yet don’t generally face sanctions for overdiagnosing. Quality measures focused on doing more may also encourage overdiagnosis in order to meet targets for remuneration incentives.[47]

An intuitive belief in early detection, fed by deep faith in medical technology is arguably at the heart of the problem of overdiagnosis. Increasingly we’ve come to regard simply being

“at risk” of future disease as being a disease in its own right. Starting with treatment of high blood pressure in the middle of the 20th century,[48] increasing proportions of the healthy population have been medicalised and medicated for growing numbers of symptomless conditions, based solely on their estimated risk of future events. Although the approach has reduced suffering and extended life for many, for those overdiagnosed it has needlessly turned the experience of life into a tangled web of chronic conditions. The cultural norm that “more is better” is confirmed by recent evidence suggesting patient satisfaction flows from increased access to tests and treatments, even though more care may be associated with greater harm.[49,50]

What can we do about overdiagnosis?

Building on existing knowledge and activity, the 2013 conference on overdiagnosis will provide a forum for learning more, increasing awareness, and developing ways to prevent the problem (www.preventingoverdiagnosis.net). Research on overdiagnosis is now recognised as part of the future scientific direction of the National Cancer Institute’s division of cancer prevention in the United States.[51] The 2013 conference hopes to provide researchers working in this field with the chance to share and debate methods and further advance research agendas. As to education, the development of a range of curriculums and information packages could help raise awareness about the risks of overdiagnosis, particularly associated with screening.[52] In association with *The BMJ*, a series of articles about the potential for overdiagnosis within specific conditions is being planned. And at the level of clinical practice new protocols are being developed to bring more caution in treating incidentalomas.[3] Similarly, some are urging that we consider raising the thresholds that define “abnormal” —in breast cancer screening, for example— and evaluate methods of observing changes to some suspected pathologies over time, rather than intervening immediately.[53] As we’ve seen, early studies of how to safely undiagnose or de-prescribe are starting to emerge.

At a policy level, reform of the process of defining disease is urgently required, with one model coming from the National Institutes of Health in the United States, where people with financial or reputational conflicts of interest are disqualified from panel membership.[20] Dispassionate assessment of evidence may result in disease definitions being narrowed, as

has been seen with the recent tentative proposals to raise thresholds for high blood pressure that could demedicalise up to 100 million people.[54] Processes for defining disease may also benefit from an attempt to synthesise the evidence from clinical medicine with literature on the wider social and environmental determinants of health. Other policy reforms could review the permanency of some diagnostic labels, address calls for increased independence in the design and running of scientific studies,[55] and adjust the structural and legal incentives driving overdiagnosis.

Concern about overdiagnosis does not preclude awareness that many people miss out on much needed healthcare. On the contrary, resources wasted on unnecessary care can be much better spent treating and preventing genuine illness. The challenge is to work out which is which, and to produce and disseminate evidence to help us all make more informed decisions about when a diagnosis might do us more good than harm.

Box 2. Examples of overdiagnosis

Asthma—Canadian study suggests 30% of people with diagnosis may not have asthma, and 66% of those may not require medications. [37]

Attention deficit hyperactivity disorder—Widened definitions have led to concerns about overdiagnosis; boys born at the end of the school year have 30% higher chance of diagnosis and 40% higher chance of medication than those born at the beginning of the year[46]

Breast cancer—Systematic review suggests up to a third of screening detected cancers may be overdiagnosed[4]

Chronic kidney disease—Controversial definition classifies 1 in 10 as having disease; concerns about overdiagnosis of many elderly people [23]

Gestational diabetes—Expanded definition classifies almost 1 in 5 pregnant women [31]

High blood pressure—Systematic review suggests possibility of substantial overdiagnosis[22]

High cholesterol—Estimates that up to 80% of people with near normal cholesterol treated for life may be overdiagnosed[3]

Lung cancer—25% or more of screening detected lung cancers may be overdiagnosed[56]

Osteoporosis—Expanded definitions may mean many treated low risk women experience net harm[18]

Prostate cancer—Risk that a cancer detected by prostate specific antigen testing is overdiagnosed may be over 60%[12]

Pulmonary embolism—Increased diagnostic sensitivity leads to detection of small emboli. Many may not require anticoagulant treatment [39]

Thyroid cancer—Much of the observed increase in incidence may be overdiagnosis[28]

Acknowledgements

We thank the participants at the April 2012 Coolangatta planning meeting on overdiagnosis: Paul Glasziou, Kirsten McCaffery, Melissa Sweet, Hilda Bastion, Andrew Wilson, Ian Scott, Suzanne Hill, Alexandra Barratt, Steve Woloshin, Lisa Schwartz, Fiona Godlee, and Rae Thomas. We also thank Julia Lowe.

Author contributions

RM conducted a scoping of the literature on overdiagnosis, initiated and developed the idea and structure for the article, completed the first draft of the manuscript, and managed the

editing and subsequent revisions. JD and DH were involved in developing the structure for the article, provided feedback suggested revisions on the first and subsequent iterations and performed some of the editing functions.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: JD is supported by NHMRC project grant 511217; they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; all authors were at the April 2012 planning meeting for the 2013 conference and RM is undertaking a PhD on overdiagnosis.

Provenance and peer review: Commissioned; externally peer reviewed.

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Chapter 3 Expanding Disease Definitions in Guidelines and Expert Panel Ties to Industry: A Cross-sectional Study of Common Conditions in the United States.

PLoS Med 2013;10(8):e1001500.

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Abstract

Background

Financial ties between health professionals and industry may unduly influence professional judgments and some researchers have suggested that widening disease definitions may be one driver of overdiagnosis, bringing potentially unnecessary labelling and harm. We aimed to identify guidelines in which disease definitions were changed, to assess whether any proposed changes would increase the numbers of individuals considered to have the disease, whether potential harms of expanding disease definitions were investigated, and the extent of members' industry ties.

Methods and Findings

We undertook a cross-sectional study of the most recent publication between 2000 and 2013 from national and international guideline panels making decisions about definitions or diagnostic criteria for common conditions in the United States. We assessed whether proposed changes widened or narrowed disease definitions, rationales offered, mention of potential harms of those changes, and the nature and extent of disclosed ties between members and pharmaceutical or device companies.

Of 16 publications on 14 common conditions, ten proposed changes widening and one narrowing definitions. For five, impact was unclear. Widening fell into three categories: creating “pre-disease”; lowering diagnostic thresholds; and proposing earlier or different diagnostic methods. Rationales included standardising diagnostic criteria and new evidence about risks for people previously considered to not have the disease. No publication included rigorous assessment of potential harms of proposed changes.

Among 14 panels with disclosures, the average proportion of members with industry ties was 75%. Twelve were chaired by people with ties. For members with ties, the median number of companies to which they had ties was seven. Companies with ties to the highest proportions of members were active in the relevant therapeutic area. Limitations arise from reliance on only disclosed ties, and exclusion of conditions too broad to enable analysis of single panel publications.

Conclusions

For the common conditions studied, a majority of panels proposed changes to disease definitions that increased the number of individuals considered to have the disease, none reported rigorous assessment of potential harms of that widening, and most had a majority of members disclosing financial ties to pharmaceutical companies.

Introduction

Changes in technologies, treatments, medical knowledge, and cultural norms provide cause to review and change disease definitions and diagnostic thresholds, a task that is commonly undertaken by expert panels, consensus meetings, or influential workgroups who publish findings as statements, special reports, or as part of clinical practice guidelines. While such changes can be beneficial, there is an increasing recognition that widening of disease definitions may be one factor contributing to the problem of overdiagnosis, occurring across a range of conditions including pulmonary embolism, breast and prostate cancers.[1,2] The concern expressed by some researchers is that for some people with milder symptoms, at lower risks, or in earlier stages of possible disease, the harms of a diagnostic label and treatment may outweigh benefits.[3,4]

At the same time there is accumulating evidence about pervasive financial ties between pharmaceutical companies and health professionals,[5] including those writing guidelines,[6] and disease definitions.[7] While noting the value of professional–industry collaborations, a 2009 Institute of Medicine (IOM) report found “widespread relationships with industry have created significant risks that individual and institutional financial interests may unduly influence professionals’ judgments,” and that these “conflicts of interest” threaten the integrity of research, the objectivity of education, the quality of patient care, and public trust in medicine.[5]

The 2009 report recommended professional societies and other organisations drafting clinical practice guidelines should “generally exclude as panel members individuals with conflicts of interest.” A subsequent 2011 IOM report on how to produce trustworthy guidelines included recommendations that “whenever possible,” guideline developers “should not have” conflicts of interest, that only a minority should have conflicts, and that chairs should be free of conflicts.[8]

As both reports make clear, in addition to financial ties there are non-financial or intellectual conflicts such as academic advancement, and there should be no assumption that having a conflict is unethical, or “that any particular professional will necessarily let financial gain influence his or her judgment”. [5]

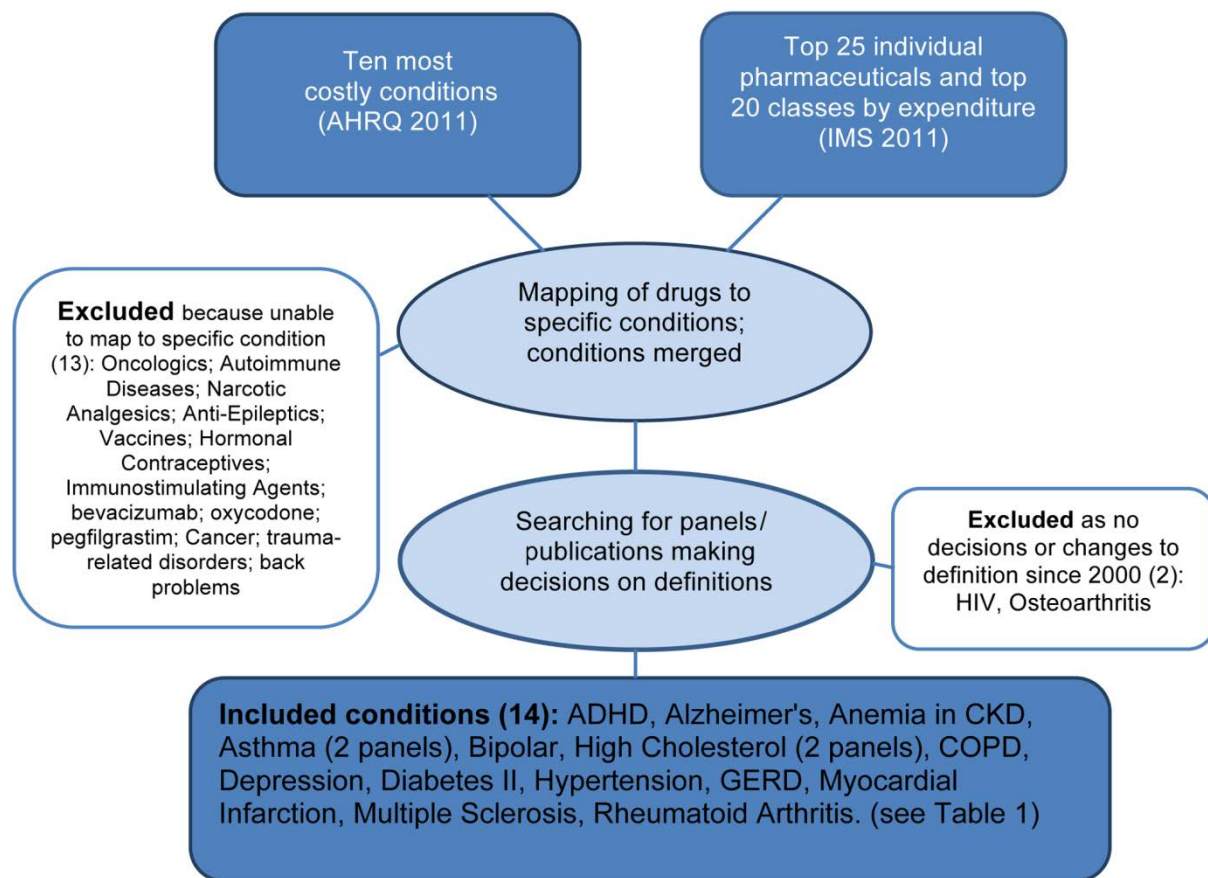
A 2011 systematic review found many clinical guideline panels have failed to disclose financial ties, and those that did disclose had a “high percentage” of individuals with financial conflicts of interest.[6] Studies analysing ties of working groups for the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, which set definitions and diagnostic criteria, have also found a majority of members with ties.[7] Kung and colleagues recently found two-thirds of individuals chairing guideline committees had conflicts of interest.[9]

Few studies[7] have examined the financial ties of members of panels reviewing and changing definitions of common conditions, whether as part of practice guideline development or other processes. Our aim was to identify guideline panels in the US setting that have most recently made decisions about definitions or diagnostic thresholds for common conditions, and to report on any proposed changes and their industry ties.

Methods

List of Conditions

On the basis of the method previously used by Choudhry and colleagues,[10] we derived a list of common conditions in the United States, drawing from a list of the ten most costly adult diseases,[11] the top 20 therapeutic classes of drugs, and the top 25 individual drugs by expenditure.[12] Consistent with that method, drugs used to treat many non-specific conditions were excluded (e.g., pain killers). For situations in which a drug was approved for a number of conditions, we identified the most common condition for inclusion (e.g., etanercept ultimately mapped to rheumatoid arthritis, not psoriatic arthritis). If a condition in the top ten costly disease list was too broad or diffuse, or covered many specific conditions, it was excluded (e.g., back problems). A flowchart of the method appears in figure 2.

Figure 2. Flowchart identifying study conditions and panels reviewing definitions.

Note: bipolar/depression was one panel.

We aimed to identify the most recent publication from panels making decisions about disease definition and diagnosis. A panel publication was eligible for inclusion if it was generated or supported by a widely recognised US-based organisation, published between 2000 and April 2013, and included deliberations and decisions on disease definitions and/or diagnostic criteria, classification, or assessment. If the panel made decisions, but proposed no changes, our search would continue for the most recent publication proposing changes, to include as well. If the focus of the panel publication was limited to specific sub-groups of patients, (e.g., adolescents), specific sub-categories of the condition (e.g., work-related asthma), it came from a single entity (e.g., a health maintenance organisation), or it included

treatment recommendations but no review and deliberation on disease definition or diagnostic criteria, it was excluded.

During a pilot phase, using the searches for the most recent hypertension and asthma panel publications, an explicit search strategy using standardized keywords was iteratively developed in order to maximise sensitivity. We searched Medline (Ovid) using terms for each disease/condition and combined these terms with a standardized search strategy consisting of a string of MeSH and keyword terms to identify panels and publications (example in Table S1). Searches were run over 26–31 July 2012, updated 17–18 April 2013, and limited to English language from 2000.

To further improve sensitivity and try to ensure recent publications were not missed, two authors (RM, GC) independently analysed the results of the standardised Medline searches for all conditions, and supplemented this with independent individual searches of the websites of the relevant National Institutes of Health and the National Guideline Clearing House. For two conditions, minor discrepancies in independent suggestions were resolved by discussion and, in one case (diabetes II), by consultation with a third author (PPG). Because of their global prominence and influence, if a panel was constituted under the umbrella of the National Institutes of Health (NIH), or the American Psychiatric Association's DSM, and met our inclusion criteria, these panels were identified for inclusion in our study. If there was a more recent panel publication that also met the study's inclusion criteria, in addition to the NIH or DSM panel, we included the more recent publication as well. This occurred twice (asthma and high cholesterol), resulting in two publications being identified for each condition.

Information on the Panels' Decisions

For each publication we extracted information on key proposed changes to definitions/diagnostic criteria, the rationale offered, and any mention of potential harms associated with the proposed changes (e.g., overdiagnosis, overtreatment, medicalising normality, labelling asymptomatic people). All six authors then made an assessment of whether the panel's proposed key changes would tend to widen (e.g., earlier diagnosis, lower thresholds, adding symptoms, increasing numbers diagnosed) or narrow the disease definition, or whether it was unclear.

Information on Industry Ties

Using published disclosure sections from the panel publications, duplicate independent extraction of data was conducted (RM and research assistant Peter Coxeter), with a third party resolving any disagreement (PG). Ties were categorized as speaker/honorarium, consultant/adviser, grant/research, stock, employee, travel, or royalties. Panel members were those listed as authors or identified as the group with primary responsibility for generating the publications. In line with the IOM approach,[5] an industry tie was defined as a tie to a pharmaceutical, diagnostic, device, or biotechnology company, but not a communications or medical education company. If there was any lack of clarity as to the nature of the company, or uncertainty if it met study criteria, a tie was not recorded. Once all industry ties were recorded for each panel, websites of companies with financial ties to the three highest proportions of panel members were searched to determine whether those companies were active in the specific therapeutic area. Where they appeared in disclosure sections, the disclosure of any ties to public agencies, non-government organizations, and publishers was also recorded.

Results

After analysing source documents,[11,12] the following drug classes, individual drugs, and conditions were excluded when identifying study conditions, as they were too non-specific or too broad, and did not map to specific conditions enabling analysis: oncologics; autoimmune diseases; narcotic analgesics; anti-epileptics; vaccines; hormonal contraceptives; immunostimulating agents; bevacizumab; oxycodone; pegfilgrastim; cancer; trauma-related disorders; and back problems.

From an initial list of 16 included common conditions, for two—osteoarthritis, HIV—we could identify no panel that made decisions about definitions or diagnostic thresholds since 2000 in the US context specifically. For the remaining 14 conditions, we identified the most recent panels that deliberated and made decisions about disease definitions, all of which proposed changes. For asthma and high cholesterol we identified two panels each, one constituted under the government funded NIH, [13,14] and one by professional societies, [15,16] reflecting the two main types of panels identified in this study. A single panel, the DSM-V Mood Disorders working group, proposed changes to two different conditions,

bipolar and depression, in two separate web-based publications.[17] A full list of the final 14 conditions, 15 panels and 16 publications, key changes and rationale, analysis of panel decisions, and disclosed ties appears in Table 2.

Table 2. Conditions and characteristics of the panels and publications included in the study.

Disease	Panel	Change/s	Rationale	Widens or Narrows?	Mentions Risk?	Discloses?	Ties?	Chair Ties?	For Members with Ties, Mean Numbers:			Percent Members Disclosing Non-Industry Ties
									Speaker/Honoraria Ties	Consultant/Adviser Ties	Research/Grant Ties	
ADHD	DSM V 2012 [19]	Changes onset age; expands symptoms	Help facilitate adult diagnosis; previous age invalid	Widen	y	y	y	n	2	1.2	1.8	78
Alzheimer	NIA-AA 2011 [28–30]	Creates new categories	Update; new evidence about biomarkers	Widen	y	y	y	y	0	4.5	0.9	13
Anemia/CKD	KDIGO 2012 [33]	Narrows definition	In line with WHO	Narrow	n	y	y	y	0.9	2.3	1.2	n/a
Asthma	ATS/ERS 2009 [15]	Redefines “severity”	Complex	Unclear	n	y	y	y	2.9	5.3	4.3	13
Asthma	EPR 3 2007 [13]	New classification; removes “mild-intermittent”	Complex	Unclear	unclear	y	y	y	3.3	6.4	4.1	39
Bipolar	DSM V 2012 [17]	Adds core symptom, new specifier	Complex	Unclear	y	y	y	y	2.1	3	1.8	83
Depression ^a	DSM V 2012	Removes bereavement exclusion	Exclusion was not justified	Widen	y							
Cholesterol ^b	ATP III 2002 [14]	Changes thresholds	Risk of future events	Widen	n	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Cholesterol	AACE 2012 [16]	Recommends additional new test	Evidence test can predict risk	Widen	n	y	y	y	3.6	2.1	1.4	n/a
COPD ^c	GOLD 2011 [18]	Changes diagnostic method and classification	Simplicity; old system inadequate	Unclear	y	y	y	y	n/a	n/a	n/a	8
Diabetes II ^d	International Expert Committee 2009 [22]	Changes diagnostic method; new cut-points	Better test; cut-point related to future risk	Unclear	y	y	n	n	n/a	n/a	n/a	n/a
GERD ^e	Montreal Definition 2006 [21]	New definition and classification	Better for research, simplify management	Widen	n	y	y	y	n/a	n/a	n/a	n/a
Hypertension	JNC7 2003 [23]	Creates new diagnostic category	Risk of future complications	Widen	n	y	y	y	4.9	6.7	6.9	27
MS	2010 Revision McDonald Criteria [42]	Changes imaging criteria for diagnosis	Simplify diagnosis, reduced testing	Widen	n	y	y	y	2.6	6.1	2.7	83
MI ^f	Universal Definition 2012 [20]	Changes to criteria and classification	Development of more sensitive tests	Widen	y	y	y	y	n/a	n/a	n/a	21
RA ^g	ACR/ELARCI 2010 [43]	New classification system	Early intervention; consistency in research	Widen	n	y	y	y	n/a	n/a	n/a	3

^aThe same Mood Disorders work group proposed separate changes to bipolar and depression.

^bThe cholesterol 2002 panel publication was silent on disclosure.

^cThe COPD panel did not separate speaker and consultant ties.

^dThe diabetes panel disclosed no ties.

^eGERD panel disclosures only pertained to one company and did not include separate categories.

^fThe myocardial infarction panel reported ties in a method that did not allow categorization of different forms of tie.

^gThe rheumatoid arthritis panel did not separate all speaker and consultant ties.

MI, myocardial infarction; MS, multiple sclerosis; n/a, not available; RA, rheumatoid arthritis.

doi:10.1371/journal.pmed.1001500.t001

Among 16 publications, all authors in our study agreed that proposals in ten publications would tend to widen definitions (Table 3) and for one, narrow the definition. For the remaining five publications the impact was unclear. Rationales for the benefits of widening definitions or expanding diagnostic categories included: evidence about the risk of future adverse events for people previously considered normal (pre-hypertension); simplification (gastroesophageal reflux disease [GERD]); standardisation for research (rheumatoid arthritis); and the emergence of new evidence about biomarkers, tests, or treatments

(Alzheimer disease). Among 15 panels, six included mention of possible harms of proposed changes (Table 4), albeit briefly, with three of those including citations in that mention,[17-19] two citing primary studies,[18,19] and one of those citing a review of primary studies as well.[18] One publication referred to the potential negative consequences for those who would be labelled by the expanded definition,[20] and only one referred to overdiagnosis.[21]

Table 3. Different ways to expand disease definitions.

Method of Widening	Disease	Details
Creating new categories of pre-disease	Hypertension	Describes pre-hypertension
	Alzheimer disease	Describes pre-dementia and defines pre-clinical Alzheimer disease
Lowering diagnostic thresholds	High cholesterol 2002	Lowers cholesterol and triglyceride thresholds
	ADHD	Changes age of onset; adds new symptoms
	Depression	Removes bereavement exclusion
	GERD	Drops severity threshold for definition
Earlier diagnosis, different diagnostic method	Rheumatoid arthritis	Earlier diagnosis
	Multiple sclerosis	Single scan diagnosis, earlier identification
	Myocardial Infarction	More sensitive tests identifying more people
	High cholesterol 2012	Additional new test

doi:10.1371/journal.pmed.1001500.t002

Table 4. Mention of possible harms of proposed changes to definitions.

Condition	Panel Comments
ADHD [19]	"main potential negative consequence of raising the age of onset is an increase in prevalence"
Alzheimer disease [30]	"ethical and practical implications" of a "diagnosis" of AD at preclinical stage "need to be studied"
COPD [18]	tests "may lead to more frequent diagnosis of COPD in older adults... as the normal process of aging affects lung volumes and flows, and may lead to under-diagnosis in adults younger than 45"
Diabetes II [22]	need to balance "stigma and costs of mistakenly identifying individuals as diabetic against the minimal clinical consequences of delaying the diagnosis in someone with an A1C level 6.5%"
Mood Disorders panel (Bipolar and Depression) [17]	to prevent "medicalization of normal fluctuations of mood" diagnoses should only be applied when the "clinician determines that the symptoms are associated with clinically significant distress or impairment that require clinical care"
Myocardial infarction [20]	"the current modification of the definition of MI may be associated with consequences for the patients and their families in respect of psychological status, life insurance, professional career..."

Note: for all other panel publications we could identify no mentions.
doi:10.1371/journal.pmed.1001500.t003

The average number of panel members was 21 (range, five to 52). Among 15 panels, 12 included members disclosing financial ties to multiple companies, one panel disclosed ties to a single company only (GERD),[21] one stated that members had no relevant conflicts of interest (diabetes II),[22] and one had no disclosure section (high cholesterol 2002),[14] also

the oldest panel. For a total of 2,081 individual ties across all categories recorded in the study, there were 55 discrepancies, 2.6%, arising from the independent extraction, mainly involving one or other extractor accidentally missing or adding a specific tie, or making errors by entering a specific tie into an adjacent column or row in a spreadsheet. All were resolved by discussion.

Among 14 panels with disclosure sections, the average proportion of members with industry ties was 75% (range 0%–100%) (Table 5). For members with ties, the median number of pharmaceutical or device companies to which they had declared ties to was seven (Table 5). For the nine panel publications disclosing multiple separate categories of tie, on average, members with industry ties were a consultant/adviser for four companies, received speaker fees/honoraria from two companies, and they or their institutions received research support from three. Twelve panels were chaired or publications led by authors with industry ties, most commonly to multiple companies. Among panels disclosing any ties to government agencies, non-government organisations, or publishers, on average around one-third of panel members disclosed these ties.

Table 5. Nature and extent of disclosed ties, by panel.

Panel	Total Number of Industry Ties by Category ^a				Percent Members with Industry Ties	Median <i>n</i> (IQR) Companies Tied to	Percent Members with Non-Industry Ties ^c
	Speaker/Honoraria	Consultant/Adviser	Grant/Research	Other ^b			
ADHD 2012 [19]	10	6	9	2	5/9 (56%)	2 (2–5)	7/9 (78%)
Alzheimer disease 2011 [28–30]	1	117	23	10	26/46 (57%)	5 (2–7)	6/46 (13%)
Anemia/CKD 2012 [33]	14	34	18	5	15/17 (88%)	3 (2–4)	n/a
Asthma 2009 [15]	67	121	99	6	23/24 (96%)	6 (5–10)	3/24 (13%)
Asthma 2007 [13]	53	103	66	0	16/18 (89%)	7 (5–11)	7/18 (39%)
Bipolar; depression 2012 [17]	17	24	14	6	8/12 (67%)	5 (3–6)	10/12 (83%)
Cholesterol 2012 [16]	25	15	10	0	7/8 (88%)	4 (3–7)	n/a
COPD 2011 ^d [18]	n/a	n/a	n/a	n/a	12/12 (100%)	9 (8–12)	1/12 (8%)
Hypertension 2003 [23]	44	60	62	2	9/11 (82%)	12 (11–13)	3/11 (27%)
MS 2010 [42]	44	104	46	9	17/18 (94%)	7 (5–10)	15/18 (83%)
MI 2012 ^d [20]	n/a	n/a	n/a	n/a	43/52 (83%)	7 (3–12)	11/52 (21%)
RA 2010 ^d [43]	n/a	n/a	n/a	n/a	17/35 (49%)	7 (5–9)	1/35 (3%)

^aIndividual members can disclose ties to more than one company.

^bOther = stock, employee, travel, royalties.

^cNon-industry ties include ties to public agencies, non-government organizations, and publishers; some disclosure sections did not include non-industry ties.

^dDisclosure sections lumped some categories together.

CKD, chronic kidney disease; IQR, interquartile range; MI, myocardial infarction; MS, multiple sclerosis; n/a, not available; RA, rheumatoid arthritis.

doi:10.1371/journal.pmed.1001500.t004

For the 12 panels for which ties were disclosed to more than one company, almost all companies with ties to the three highest proportions of panel members were also active in the market for that panel's condition, with at least one drug on the market or in the research pipeline (Table 6). For example, with the chronic obstructive pulmonary disease [COPD]

publication, Astra Zeneca, Boehringer-Ingelheim, and GSK—all companies with drugs for the condition—each had financial ties to 11 of 12 members, including the chair.[18] With the DSM-V Mood Disorders work group, Pfizer and Lilly—with drugs for depression and bipolar—had ties to five of the 12 members.[17] Similarly, companies marketing hypertension drugs—Bristol-Myers Squibb, Merck, Novartis—each had financial ties to eight of the 11 members of the panel which created the new diagnostic category “pre-hypertension”.[23]

Table 6. Companies with highest proportions of ties, and drugs in therapeutic area.

Panel ^a	Top Companies	n and Percent of Panel to Which Company Had Ties	Drug in Therapeutic Area
ADHD [19]	Janssen Cilag	3/9 (33%)	Methylphenidate HCl
	Eli Lilly	2/9 (22%)	Atomoxetine HCl
	McNeil	4/9 (44%)	Methylphenidate HCl
	Shire	2/9 (22%)	Amphetamine (Adderall)
Alzheimer disease [28–30]	Pfizer	13/46 (28%)	Donepezil HCl
	Eli Lilly	14/46 (30%)	Solanezumab
	Elan	11/46 (24%)	Bapineuzumab
Anemia/CKD [33]	Amgen	13/17 (76%)	Darbepoetin alfa
	Roche	5/17 (29%)	Methoxy polyethylene glycol-epoetin beta
	Affymax	5/17 (29%)	Peginesatide
	Vifor	4/17 (24%)	Iron supplementation
Asthma 2009 [15]	GSK	20/24 (83%)	Fluticasone propionate
	AZ	19/24 (79%)	Zafirlukast
	Novartis	14/24 (58%)	Omalizumab
Asthma 2007 [13]	AZ	11/18 (61%)	Zafirlukast
	GSK	12/18 (67%)	Fluticasone propionate
	Merck	13/18 (72%)	Montelukast sodium
Bipolar/depression [17]	AZ	3/12 (25%)	Quetiapine fumarate
	Lilly	5/12 (42%)	Duloxetine; olanzapine
	Pfizer	5/12 (42%)	Sertraline HCl; ziprasidone HCl
Cholesterol 2012 [16]	Merck	4/8 (50%)	Simvastatin
	Abbott	3/8 (38%)	Niacin
	AZ	3/8 (38%)	Rosuvastatin
	Novo-Nordisk	3/8 (38%)	n/a
COPD [18]	AZ	11/12 (92%)	Budesonide & formoterol fumarate dihydrate
	BI	11/12 (92%)	Tiotropium bromide
	GSK	11/12 (92%)	Fluticasone propionate
Hypertension [23]	BMS	8/11 (73%)	Irbesartan
	Merck	8/11 (73%)	Losartan
	Novartis	8/11 (73%)	Amlodipine besylate/benazepril hydrochloride
Myocardial infarction [20]	AZ	23/52 (44%)	Rosuvastatin
	Merck	16/52 (31%)	Simvastatin
	Bayer	15/52 (29%)	Rivaroxaban
	BI	15/52 (29%)	Alteplase
Multiple sclerosis [42]	Biogen	13/18 (72%)	Interferon beta-1a
	Merck Serono	12/18 (67%)	Interferon beta
	Sanofi	11/18 (61%)	Teriflunomide
Rheumatoid arthritis [43]	UCB	15/35 (43%)	Certolizumab pegol
	Abbott	14/35 (40%)	Adalimumab
	BMS	13/35 (37%)	Abatacept

^aAnalysis not possible for Cholesterol 2002, diabetes, GERD panels.
 CKD, chronic kidney disease; n/a, not available.
 doi:10.1371/journal.pmed.1001500.t005

To evaluate any potential impact of the IOM recommendations regarding industry ties, we compared the panel publications released in 2012—after both IOM reports, [5,8]—to those released earlier. We found similar proportions of members disclosing industry ties (76% was the average across 2012 panels; 74% was the average across pre-2012 panels); a small reduction in the median number of companies to which those members disclosed ties in the

2012 panels (four in 2012 panels; seven pre-2012 panels); and similar proportions of panel publications widening definitions (four of six of 2012 publications; six of ten of pre-2012 publications).

Discussion

In this cross-sectional analysis of panels making recent decisions on definitions of common conditions in the US context, we found most panels proposed widening definitions and most had a majority of members with multiple ties to pharmaceutical companies. Proposals to widen fell into three inter-related categories: creating new categories of “pre-disease”; lowering diagnostic thresholds; and proposing earlier diagnosis or different diagnostic methods (Table 3). In some cases a clear rationale was offered for these changes—as when the hypertension panel cited evidence from original studies and meta-analysis linking normal blood pressure with elevated risks as the reason to create “pre-hypertension”.[23] In other publications, including the 2007 panel proposing changes to the diagnosis of asthma,[13] the rationale was less clear, more complex and diffuse.

Notwithstanding the problem of under-diagnosis, a growing body of evidence suggests overdiagnosis may be occurring across a range of common conditions, including hypertension,[24] asthma,[25] attention deficit hyperactivity disorder (ADHD),[26] and COPD.[27] Yet less than half of the study publications mentioned potential harms of proposed changes to definitions, and none included a rigorous evidence-informed discussion of those risks or how they might be mitigated.

In a three-part publication in 2011,[28-30] proposing new categories of “pre-clinical” Alzheimer disease (for research only at this stage) and “predementia”—which would clearly expand the population labelled—there was one short reference to the need to study the “ethical and practical implications” of diagnosing people at a “preclinical” stage.[30] The panel proposing changes to assessment and classification of COPD briefly mentioned that diagnostic methods “may lead to more frequent diagnosis of COPD in older adults with mild COPD as the normal process of aging affects lung volumes and flows”,[18] but did not explicitly refer to the risk of “overdiagnosis” as it had done in a previous version of its report.[31] Proposing changes to ADHD diagnostic criteria—in part to make the condition

more amenable to being a “lifespan” disorder involving adults as well as children—the DSM-V panel mentioned potential increases in prevalence but suggested they would be “negligible” (Table 4).[32]

Among panels disclosing ties, almost all chairs had financial ties to industry, and an average of three-quarters of members had ties to a median of seven companies, commonly working as consultants, advisers and/or speakers, as well as receiving research support. Companies with financial relationships with the greatest proportion of panel members were marketing or developing drugs for the same conditions about which those members were making critical judgements. GSK for example, marketing top-selling products for asthma, had financial ties to 20 of the 24 members of the 2009 asthma panel, and all 20 were consultant/advisers and/or declared speaker/honoraria ties to GSK.[15]

This study has several important limitations. First, the lack of a comparison group means it is impossible to draw any inference of association between frequency of industry ties and proposals to change disease definitions. The exclusion of common conditions too broad to enable a focussed analysis of single panel publications (e.g., back problems) means it may have missed potentially important examples of changing disease definitions and limits generalizability of findings. The focus on the United States—chosen explicitly because of its globally influential panels such as DSM-V workgroups—also limits generalizability. A fourth limitation is reliance solely on disclosed ties, likely leading to an underestimate of their extent. Finally, we note that while we tried to ensure an exhaustive and multi-layered search strategy, we are unaware of any established method for identifying panel publications that review or propose changes to disease definitions.

Notwithstanding these limitations, the study has strong clinical, research, and policy relevance. Its novel focus on panels reviewing and proposing changes to common disease definitions or diagnostic criteria will help deepen understanding of the nature of what's been described as the “modern epidemic” of overdiagnosis.[2] Moreover, the group of 16 publications includes influential articles affecting the definition of 14 common conditions and impacting directly on medical policy and practice around the world.

The study findings are consistent with and help augment the evidence-base about industry ties of influential medical professionals. The 2011 systematic review found 56%–87% of clinical guideline writers had conflicts of interest,[6] similar to our finding of 75% across disease-defining panels. Kung and colleagues found 71% of guideline committee chairs had conflicts,[9] again similar to our findings. While these proportions may reflect the level of ties among medical specialists more generally, they are in stark contrast to IOM 2009 and 2011 reports calling for panels to generally exclude people with conflicts of interest.[5,8] As reported above, we found no change in the proportion of members disclosing ties in the 2012 publications, after release of both IOM reports.

At least two publications,[20,21] made reference to members believing industry ties did not influence their decision-making, and we make no suggestion to the contrary. Indeed our data do not support any inference industry ties are associated with widening definitions or failure to rigorously assess potential harms of that widening. With anemia in chronic kidney disease, a panel with a high proportion of ties raised thresholds, effectively narrowing the definition.[33] There will doubtless be other cases where diseases have been widened by panels of medical specialists without industry ties. Moreover, as Lurie and colleagues found in the context of drug regulation, the financial conflicts of expert advisory committees did not correlate significantly with their voting outcomes.[34] Medicalisation and overdiagnosis are driven by many factors—technological, professional, commercial, legal, and cultural.[3]

While inferences of association or causation between industry ties and expanding disease definitions cannot be drawn, our findings can be considered in the context of broader evidence about potentially distorting biases associated with widespread industry sponsorship and financial ties in medical research,[35-37] education,[38] and practice,[5] and in relation to “key opinion leaders” who speak and consult for industry.[39]

In 1999 Schwartz and Woloshin found changes to definitions of high blood pressure, high cholesterol, diabetes, and overweight would “dramatically inflate disease prevalence” and “ultimately label 75% of the adult U.S. population as diseased”.[40] They concluded the “extent to which new ‘patients’ would ultimately benefit from early detection and treatment of these conditions is unknown. Whether they would experience important physical or psychological harm is an open question.” To what extent newly created “patients” produced

by widening disease definitions will experience important harms remains a largely unanswered question, over a decade later.

This study did not investigate the merits of the proposed changes to the conditions identified. However, findings that diagnostic thresholds are being lowered by panels dominated by those with financial ties to multiple companies that may benefit directly from those decisions raise questions about current processes of disease definition. While it may be more difficult to locate senior specialists without industry ties, two recent IOM reports have encouraged such a change,[5,8] and models already exist for panels free of such conflicts, including the NIH consensus development program.[41]

Several unanswered questions arise from this study, which could benefit from further investigation. Researchers might fruitfully examine how definitions are changing over time, what dollar amounts are being received from industry by panel members and organisations that auspice them, and how panel proposals impact on potential markets of sponsors. Most importantly enhanced research and policy attention might be directed at designing new processes for reviewing disease definitions, free of financial conflicts of interest and informed by rigorous analysis of benefits and harms.

Supplemental Table S1: Asthma Search Strategy

Database: Ovid MEDLINE(R) <1946 to July Week 2 2012>

Search Strategy: Asthma

- ```

1 consensus/ (3929)
2 exp guideline/ (22675)
3 (consensus or report or recommend* or "position paper" or statement or guidance or
guideline*).ti. (397131)
4 or/1-3 (407005)
5 ((expert* or advisory or scientific or review or national or working or professional or
governing) adj3 (panel or group or meeting or conference or committee or board or agenc*
or body)).tw. (50995)
6 (taskforce or "working party" or association or societ*).tw. (774846)
7 5 or 6 (816637)
8 4 and 7 (36140)
9 exp *Asthma/ (80805)
10 exp Asthma/cl, di [Classification, Diagnosis] (13608)

```

|    |                                                             |
|----|-------------------------------------------------------------|
| 11 | (asthma* and (class* or diagnos* or defin*)).tw. (21202)    |
| 12 | asthma.ti. (56667)                                          |
| 13 | or/9-12 (92056)                                             |
| 14 | 8 and 13 (314)                                              |
| 15 | limit 14 to (english language and yr="2000 -Current") (154) |

### **Acknowledgments**

We would like to thank Elaine Beller and Rae Thomas at the Centre for Research in Evidence-Based Practice, Faculty of Health Sciences and Medicine, Bond University for assistance in design and analysis; Sarah Thorning, from the same centre, for assistance with development of the search strategy; and research assistant Peter Coxeter from the same centre for independent extraction of disclosure material. We thank David Henry for his comments on an early draft of this manuscript.

### **Author Contributions**

Conceived and designed the experiments: RM GC JD LB SH PG. Analyzed the data: RM GC JD LB SH PG. Wrote the first draft of the manuscript: RM. Contributed to the writing of the manuscript: RM GC JD LB SH PG. ICMJE criteria for authorship read and met: RM GC JD LB SH PG. Agree with manuscript results and conclusions: RM GC JD LB SH PG.

### **Competing interests**

RM, JD, and PG are involved in planning an international conference called Preventing Overdiagnosis. GC is a board member of General Practice Education and Training, Ltd; a registrar for the Medical Administration of the Princess Alexandra Hospital in Brisbane, Australia; and a former board member of the Royal Australian College of General Practitioners. SH is a member of the PLOS Medicine editorial board and chairs the Australian Pharmaceutical Benefits Advisory Committee, an independent advisory body for the Australian government. LB declares that no competing interests exist.

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## **Chapter 4 Chronic kidney disease controversy: how expanding definitions are unnecessarily labelling many people as diseased**

***BMJ 2013;347:f4298***

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## Summary

- *Clinical context*—Concern about the late presentation of kidney disease and missed opportunities for earlier intervention
- *Diagnostic change*—A novel framework defining and classifying “chronic kidney disease” (CKD) introduced in 2002 and modified in 2012, based largely on laboratory measurements of kidney function and damage
- *Rationale for change*—Identifying chronic kidney disease early would slow progression towards total kidney failure and provide an opportunity to prevent associated illness, particularly cardiovascular disease
- *Leap of faith*—Identifying, monitoring, and treating the newly described chronic kidney disease will improve survival and quality of life
- *Increase in disease*—The new definition labels over 1 in 8 adults (around 14%) as having chronic kidney disease. Before 2002 the lack of a consistent definition made prevalence estimates unreliable, but one US study suggested a figure of 1.7% of the population.
- *Evidence of overdiagnosis*—The combination of the large numbers now labelled as having chronic kidney disease with low rates of total kidney failure suggest many of those diagnosed will never progress to symptomatic forms of kidney disease
- *Harms from overdiagnosis*—Psychological effect of a disease label and the burden and costs of repeated assessment, testing, and potentially unnecessary treatment
- *Limitations*—Lack of prospective data evaluating the benefits and harms of testing for, monitoring, and treating the early stages of chronic kidney disease
- *Conclusions*—Clinicians should be sceptical about the current definition of chronic kidney disease and cautious about labelling patients, particularly older people

In 2002 the United States Kidney Foundation launched a novel framework for defining and classifying chronic kidney disease.[1] The framework was widely embraced because it imposed order in a chaotic landscape characterised by a variety of names, including renal insufficiency, renal impairment, and renal failure. It has had an appreciable effect on clinical care worldwide through guidelines,[2] pay for performance measures,[3] and sparked debate on the merits of screening programmes.[4] However, it has also generated considerable controversy.[5-7] We examine the rationale for the framework, the varying responses and controversies it has provoked, and provide advice for clinicians who are being faced with an increasing number of people categorised as having chronic kidney disease.

### **Changes in definition and diagnostic criteria**

Two centuries ago Bright's description of the associations between kidney disease and albumin in the urine of patients with dropsy was hailed as one of the first practical modern aids to diagnosis. Starting with Homer Smith in the 1930s, estimates of "renal clearance" emerged as measures of kidney function, leading most recently to the development of equations using various serum biomarkers, such as creatinine or cystatin C, for estimating the glomerular filtration rate (GFR).

The 2002 framework uses the term "chronic kidney disease" to include conditions that affect the kidney, with the potential to cause either progressive loss of kidney function or complications resulting from decreased kidney function. Chronic kidney disease was defined as the presence of kidney damage or decreased kidney function for three months or more, irrespective of the cause.[1] It relies largely on two laboratory measures: an estimate of glomerular filtration rate (eGFR) based on serum creatinine or cystatin C levels and an assessment of kidney damage, derived from a range of tests, most commonly increased albumin in the urine (albuminuria). A single threshold for eGFR,  $<60$  ml/min/1.73 m<sup>2</sup> uncalibrated for age or sex, was arbitrarily adopted to define chronic kidney disease. Similarly,  $\geq 3$  mg albumin/mmol creatinine in a random urine sample identified albuminuria. Initially, the framework set out five stages of chronic kidney disease, largely based on eGFR, ending with total kidney failure or end stage renal disease. Modifications followed, with

2012 guidelines dividing stage 3 (eGFR 30-59 ml/min/1.73 m<sup>2</sup>) into 3A (30-44 ml/min/1.73 m<sup>2</sup>) and 3B (45-59 ml/min/1.73m<sup>2</sup>) and adding three extended categories for persistent albuminuria (fig 3).[8] These are in line with previous changes made in the classification adopted by the National Institute for Health and Care Excellence (NICE) in the UK.[2]

**Figure 3: Prevalence of chronic kidney disease in the US by 2012 classification.**

|                                              |     |                                  | Persistent albuminuria categories |                      |                    |     |       |
|----------------------------------------------|-----|----------------------------------|-----------------------------------|----------------------|--------------------|-----|-------|
|                                              |     |                                  | A1                                | A2                   | A3                 |     |       |
|                                              |     |                                  | Normal to mildly increased        | Moderately increased | Severely increased |     |       |
|                                              |     |                                  | <3 mg/mmol                        | 3-30 mg/mmol         | >30 mg/mmol        |     |       |
| GFR categories (mL/min/1.73 m <sup>2</sup> ) | G1  | Normal or high                   | ≥90                               | 55.6                 | 1.9                | 0.4 | 57.9  |
|                                              | G2  | Mildly decreased                 | 60-89                             | 32.9                 | 2.2                | 0.3 | 35.4  |
|                                              | G3a | Mildly to moderately decreased   | 45-59                             | 3.6                  | 0.8                | 0.2 | 4.6   |
|                                              | G3b | Moderately to severely decreased | 30-44                             | 1.0                  | 0.4                | 0.2 | 1.6   |
|                                              | G4  | Severely decreased               | 15-29                             | 0.2                  | 0.1                | 0.1 | 0.4   |
|                                              | G5  | Kidney failure                   | <15                               | 0.0                  | 0.0                | 0.1 | 0.1   |
|                                              |     |                                  |                                   | 93.2                 | 5.4                | 1.3 | 100.0 |

Data on 18 026 adults from the National Health and Nutrition Examination Survey 1999-2006. Values in cells do not total to values in margins because of rounding. Green=low risk (if no other markers of kidney disease, no CKD), yellow=moderately increased risk, orange=high risk, red=very high risk. Reproduced with permission[8]

### Rationale for change

The stimulus for the 2002 framework was the absence of an agreed definition and classification of kidney disease and evidence that people were experiencing avoidable harm through late presentation of serious kidney disease, including disproportionate numbers of African Americans,[4] and the Australian aboriginal community.[9]

A key rationale for the new definition arises from evidence showing decreased eGFR and albuminuria are associated with increased risk of death or end stage renal disease.[10] The CKD Prognosis Consortium, an international research group, conducted a meta-analysis of published data from over two million people and concluded that “measures of kidney function and damage are independently associated with mortality and end stage renal disease regardless of age across a wide range of populations.”[10] A second and related rationale comes from meta-analyses showing that reduced eGFR or albuminuria were consistently associated with cardiovascular mortality.[11, 12]

The assumption was made that earlier identification and treatment could slow, stop, or reverse progression towards end stage renal disease.[1] The 2002 guidelines stated that treating early chronic kidney disease is “effective in slowing the progression toward kidney failure,” with optimism largely directed at patients with more severe forms of specific kidney diseases manifested by marked proteinuria or rapidly declining eGFR.[1] A decade later, however, the National Kidney Foundation website stated that a suite of claims about benefits of early detection and treatment of generic chronic kidney disease “remains to be proven in appropriately powered randomized trials.”[13] Similarly, the US Preventive Services Task Force, which recently found there was insufficient evidence to recommend general population based screening, reported that although identifying and treating chronic kidney disease may affect outcomes for people with established specific conditions, including diabetes or hypertension, there were no studies on the benefits of early treatment in people without them.[4]

### **Who developed the framework?**

The framework was drawn up and published in 2002 by the Kidney Disease Outcomes Quality Initiative under the auspices of the US National Kidney Foundation. The guideline that launched the framework was supported by a pharmaceutical company.[14] In the face of confusion and criticism of the potential for the framework to lead to overdiagnosis, specialist international meetings were held in 2004, 2006, and 2009 to discuss modifications. In 2012 new guidelines reaffirmed the key elements of the 2002 guidelines, with modifications including dividing eGFR based stage 3 into 3A and 3B subcategories and formally adding three extended categories for albuminuria to the diagnostic matrix.[8] Nine of the 16 working group members who produced the 2012 guidelines declared financial ties to drug or device companies, though they stated every effort was taken “to avoid any actual or reasonably perceived conflicts of interest.”[8] The body responsible for developing the guidelines has disclosed funding from a consortium of pharmaceutical or device manufacturers, though not for the “development of specific guidelines.”[8]

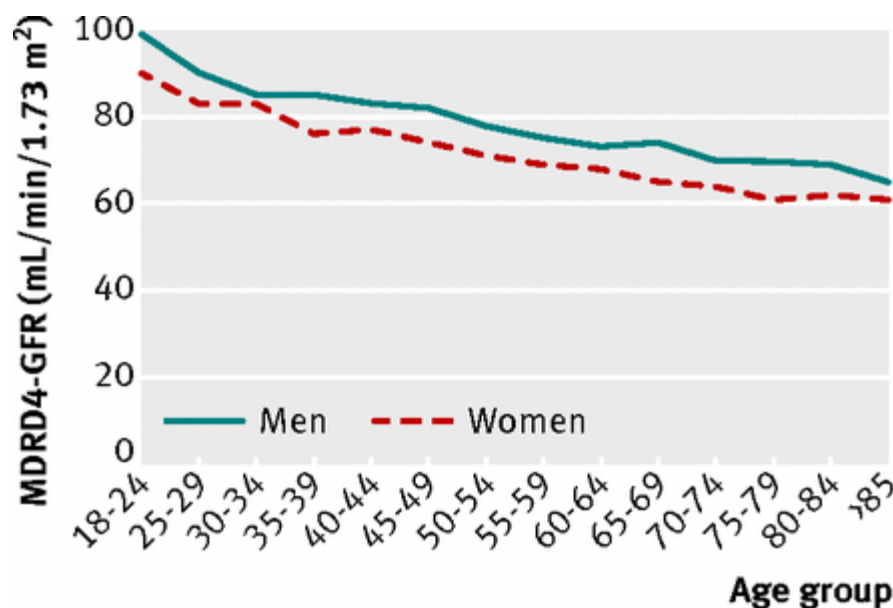
### **Effect of framework on disease prevalence**

Although it has long been recognised that kidney function declines with age and differs for men and women (fig 4), the threshold eGFR chosen to define disease was set at 60 ml/min/1.73 m<sup>2</sup>, about half that of the normal level of a young adult.[8] Under the 2002

framework anyone with an eGFR below 60 mL/min/1.73 m<sup>2</sup> for three months or longer can be diagnosed as having chronic kidney disease stage 3A or greater, irrespective of their age or sex and even if they have no other overt signs of kidney damage, such as moderate or severe albuminuria.

**Figure 4. Median eGFR rates for healthy white men and women by age.**

Redrawn with permission[5]



The adoption of this definition has resulted in more than 1 in 8 adults (almost 14%) in the US being labelled as having chronic kidney disease[8,15] and as many as 1 in 6 adults in Australia.[16] Before the 2002 framework, estimates of prevalence varied widely depending on which threshold and definition was being used. For example, one study published in 2001, which used abnormal serum creatinine values (adjusted for sex) persisting for three months or more in people enrolled in a health maintenance organisation, estimated that 4.2 million Americans (1.7%) had chronic kidney disease.[17]

At least a third of the people who meet the new definition of chronic kidney disease are classified as stage 3A.[8] Most of them are older than 65 years of age, with more women than men, and many will have an eGFR that falls within the normal range (5th to 95th percentile)

for their age.[5] Around three quarters of these have no urine markers of kidney damage, such as albuminuria.[18]

### **Response to the framework**

The chronic kidney disease framework has been adopted by groups in many countries including the United States, Australia,[19] and the United Kingdom.[2] One organisation has made substantial modifications to the framework. Kaiser Permanente in Southern California has adapted the framework using a formula to take age into account,[20] reducing the prevalence of chronic kidney disease in its insured population to about 3% compared with the almost 14% estimate arising from the framework definition.

### **Evidence of overdiagnosis**

The use of a single threshold of an eGFR of 60 ml/min/1.73 m<sup>2</sup> without calibrating it for age or sex means that around half of people aged 70 years or more are being labelled or at risk of being labelled as having chronic kidney disease.[21] However, Dutch researchers have shown that an eGFR of 60 ml/min/1.73 m<sup>2</sup> is “within the normal reference range” for men over 60 years and women over 50 years and “cannot be used to define a diseased population.”[5]

Advocates of the definition claim that “early detection can help prevent the progression of kidney disease.”[22] But while 1 in 8 adults in the US may now be labelled as having chronic kidney disease, only around 1 in 3000-5000 are being newly treated for end stage renal disease each year.[15] In a study in a Norwegian county published in 2006, which surveyed 65 000 members of the general population with a median age of 49 less than 1% of people with an eGFR of 45-59 ml/min/1.73 m<sup>2</sup> (stage 3A disease) went on to develop end stage renal disease after eight years of follow-up.[23] Based on this, it is estimated that thousands of people with stage 3A disease may need to be treated to prevent one case of end stage disease,[24] raising questions about opportunity costs to health systems. A systematic review of screening and treatment concluded that although some treatments reduced the risk of end stage renal disease in selected patients with chronic kidney disease, “many of these patients may already warrant treatment with these therapies regardless of CKD status.”[25]

Although early detection might benefit some people, by labelling so many people at low risk of symptoms as having chronic kidney disease, the new definition axiomatically produces overdiagnosis: “like a fishing trawler it captures many more innocent subjects than it should.”[26] The current definitions may misclassify at least 30% of elderly people as having stage 3 disease,[18] with those classified as stage 3A without albuminuria at highest risk of overdiagnosis.

**Concern among primary care physicians and specialists**

Primary care doctors have expressed concern about the framework (Inside Health, BBC Radio 4, 15 August 2012),[24] and a qualitative research study conducted in a representative group of general practitioners and practice nurses across England found nearly all had “reservations as to whether CKD was really a disease,” with some expressing concern about the medicalisation of the ageing process and the attendant potential for unintended harm.[27] The website of the United Kingdom National Kidney Foundation, a charitable patient organisation, explains that “Often CKD is only a very slight abnormality in the kidneys” and that “many of the elderly people with CKD may . . . have normal ageing of their kidneys.”[28]

**Uncertainties about what the evidence shows**

Acknowledging concern about the risk of overdiagnosis, proponents have continued to defend the use of an eGFR threshold of  $<60 \text{ ml/min/1.73 m}^2$  to define chronic kidney disease by referring to the meta-analyses showing its associations with end stage renal disease and cardiovascular and all-cause mortality.[10-12] Although these analyses provide complex and important evidence, they are open to differing interpretations.[29,30] Some argue that the meta-analysis of data on end stage renal disease “neither supports nor refutes” the use of the  $60 \text{ ml/min/1.73 m}^2$  threshold uncalibrated for age and sex for delineating chronic kidney disease.[31]

In relation to the associations with cardiovascular disease, questions remain about the extent to which a diagnosis of chronic kidney disease—as currently defined—adds meaningfully to the traditional assessment of risk,[32, 33] and whether these associations justify current laboratory based thresholds to diagnose chronic kidney disease. Firstly, in terms of uncertainty, estimations of such associations have important limitations, including

establishing appropriate reference points for comparisons, problems with standardising measurement, and a lack of a uniform protocol across study cohorts.[11,12] Secondly, some studies suggest that the designation of chronic kidney disease may not meaningfully add to the predictive ability of traditional cardiovascular risk factors.[33-35] For example, Angelantonio and colleagues found the clinically relevant incremental gain provided by chronic kidney disease was “about a sixth that provided by history of smoking.”[33]

### **Uncertainties about the reliability of laboratory measurements**

Although new estimating equations have improved the precision and reliability of eGFR measurements, problems with inaccuracy remain.[21] This is one reason why the framework requires that abnormal measurements persist for three months or more.[7] However, because eGFR levels can change over time, it is likely that many people would not be categorised as having chronic kidney disease if a longer period were required before diagnosis. A Norwegian study involving measurements from over 38 000 patients suggests that if the definition of disease required that an abnormality persists for 12 months, this could reduce the prevalence of stage 3 disease by 37%.[7]

There is also uncertainty about what concentration of albumin in the urine constitutes clinically “meaningful” kidney damage and how levels contribute to increased risk of future adverse events. Moderate albuminuria (defined as a urine albumin to creatinine concentration ratio of 3-30 mg/mmol (30-300 mg/g) and formerly known as microalbuminuria) is not pathognomonic of persisting chronic kidney damage. It can be transitory and is affected by many extraneous factors, including high fever, vigorous exercise, smoking, obesity, medications, and diet.[36] A third of people who are identified as having kidney damage on the basis of moderate microalbuminuria may shed that label when re-tested up to two months later.[37]

### **Potential harms from overdiagnosis**

The United States Preventive Services Task Force identified the most important potential harm of screening as “Patients could be falsely identified as having CKD and receive unnecessary treatment and diagnostic interventions.”[4] Management of early disease mostly consists of tight management of blood pressure, and as the task force has pointed out the potential benefits of identifying and treating people at risk of cardiovascular disease



through any screening programme for chronic kidney disease have to be weighed against the harms from the side effects of drugs and the risk of bringing blood pressure to excessively low levels.[4] In addition there is concern about the adverse effects of labelling healthy and asymptomatic people as having chronic kidney disease.[38,24,27] Studies of hypertension suggest that more disease labelling could increase psychological distress, absenteeism from work, and decrease quality of life.[39]

### **Cost implications**

More routine reporting of kidney function since the advent of the 2002 framework has substantially increased specialist referrals for chronic kidney disease, with referrals up 60% within a single NHS trust covering a population of 560 000 people, according to a University of Cardiff study,[40] and up 40% in two hospitals in Brisbane, Australia.[41] In the United Kingdom general practitioners have been asked to form registers of those with chronic kidney disease and monitor people. An analysis of the cost and benefits of moving to reporting eGFR in routine blood analyses by den Hartog and colleagues found a far higher number of patients falsely diagnosed with chronic kidney disease and that “any small benefit in cost effectiveness was offset by potential adverse consequences of incorrectly diagnosing CKD.”[42]

### **How to do better**

It is not clear that the current markers of early renal dysfunction, either eGFR or microalbuminuria, are useful in identifying those patients who are at most risk of symptomatic renal disease. Further research is needed to better identify which patients are at greatest risk of a modifiable form of chronic kidney disease that without intervention would progress to symptomatic advanced disease. Until better methods are available, we suggest that clinicians consider the age of the patient and the trajectory of eGFR or urinary albumin test results, and acknowledge to patients that at the moment it is uncertain whether mildly reduced renal function in the absence of other risk factors should be treated or not (see box 3). If a patient is found to have reduced renal function on a single test, the current guidance to confirm the result with another test soon after the first and that another test should be conducted after three months, should be followed.

**Conclusions**

The benefits, harms, and costs of testing, monitoring, and treating the increased number of people being identified as having chronic kidney disease need to be established by prospective studies. Meanwhile the risk of overdiagnosis warrants greater professional scrutiny and more public awareness. Clinicians should be careful not to apply disease labels to the many older people whose eGFR falls within the definition of chronic kidney disease but who are at very low risk of developing clinical problems. The fact that Kaiser Permanente explicitly attempted to avoid labelling “low risk elderly” people and adopted a higher threshold reinforces the argument for reviewing the 2012 framework. A review should be conducted by a panel with broad representation from specialty and primary care, population health, patient organisations, and civil society with minimal conflicts of interest. It is in everyone’s interest to find the best way to maximise prevention of kidney disease and its consequences while minimising the risks and cost of overdiagnosis.

**Box 3. Suggestions for clinicians**

Be informed about the controversy and debate over methods used to define chronic kidney disease

Share uncertainty about appropriateness of diagnostic thresholds and reliability of measurements with patients

Look for other changes that support the diagnosis—for example, is there evidence of anaemia, abnormal urinalysis results, or abnormalities on renal ultrasonography?

Be aware of the variability in measures of kidney function (eGFR and albuminuria) and the need to repeat the test to confirm reduced renal function

Don’t routinely use the label chronic kidney disease for people aged 65 years and older with eGFR stage 3A and no albuminuria

Older people with stable but modestly reduced eGFR (45-59 ml/min/1.73 m<sup>2</sup>) are unlikely to have a high risk of future adverse events unless they have persistent overt albuminuria

*This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies.*

**Author contributions**

RM initiated the idea for the article, conducted an examination of the literature on the controversy over the definition of chronic kidney disease, completed the first draft of the manuscript, and managed and led all subsequent revisions and iterations. RG and JD provided detailed feedback and suggested revisions on the first draft and all subsequent iterations and performed some of the editing functions.

**Competing interests**

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests. JD and RM have received support from an NHMRC STEP grant, and are helping to organise the preventing overdiagnosis conference, supported by BMJ and Consumer Reports. RM has been advising on the BMJ Too Much Medicine series. RJG provides consultation to a number of pharmaceutical companies, none directly involved in providing care for end stage renal disease. He is a medical adviser to American Renal Associates, a US provider of dialysis. He also receives honorariums for engaging in educational activities for the American Society of Nephrology and UpToDate (a Wolters-Klewer Company).

**Provenance and peer review:** Commissioned; externally peer reviewed.

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## **Chapter 5 Public opinions about overdiagnosis: a national community survey.**

**In Press, *PLOS ONE*, May 2015**

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## Abstract

### Background

Despite evidence about the "modern epidemic" of overdiagnosis, and expanding disease definitions which medicalise more people, data are lacking on public views about these issues. Our objective was to measure public perceptions about overdiagnosis, and views about financial ties of panels setting disease definitions.

### Methods and Findings

We conducted a 15 minute Computer Assisted Telephone Interview with a randomly selected community sample of 500 Australians in January 2014. We iteratively developed and piloted a questionnaire, with a convenience sample(n=20), then with participants recruited by a research company(n=20). Questions included: whether respondents had been informed about overdiagnosis; opinions on informing people; views about financial ties among panels writing disease definitions.

Our sample was generally representative, but included a higher proportion of females and seniors, typical of similar surveys. American Association for Public Opinion Research response rate was 20% and cooperation rate, 44%. Only 10% (95% CI 8%-13%) of people reported ever being told about overdiagnosis by a doctor. 18% (95% CI 11%-28%) of men who reported having prostate cancer screening, and 10% (95% CI 6%-15%) of women who reported having mammography said they were told about overdiagnosis. 93% (95% CI 90%-95%) agreed along with screening benefits, people should be informed about overdiagnosis. On panels setting disease definitions, 78% (95% CI 74%-82%) felt ties to pharmaceutical companies inappropriate, and 91% (95% CI 82%-100%) believed panels should have a minority or no members with ties. Limitations included questionnaire novelty and complexity.

### Conclusions

A small minority of Australians surveyed, including those reporting being screened for prostate or breast cancer, reported being informed of overdiagnosis; most believed people should be informed; and a majority felt it inappropriate doctors with ties to pharmaceutical companies write disease definitions. Results suggest strategies to better inform people about overdiagnosis, and review disease definition processes, have significant public sympathy.

## Introduction

The “modern epidemic” of overdiagnosis is now recognised as an important risk to health,[1,2] with evidence-based efforts underway to combat it.[3] Overdiagnosis occurs when someone is diagnosed with a disease that would not have harmed them,[2] often as a result of undergoing screening, and evidence is emerging that many people are overdiagnosed and labelled unnecessarily across a range of conditions.[4] An inquiry in the United Kingdom estimated 19% of the breast cancers detected during mammography screening may be overdiagnosed,[5] and the United States Preventive Services Task Force recently noted there is “convincing evidence that PSA-based screening leads to substantial overdiagnosis of prostate tumors”, with estimates ranging from 17% to 50%.[6]

While there is on-going scientific discussion about the best methods for measuring overdiagnosis, and debates about strategies for reducing avoidable overdiagnosis without increasing under-diagnosis, there is now official recognition of the need for greater awareness of the problem. As a working group convened under the auspices of the National Cancer Institute has observed, “Physicians, patients, and the general public must recognize that overdiagnosis is common and occurs more frequently with cancer screening”.[7]

Screening programmes are one of many causes of overdiagnosis including technological changes enabling detection of ever-smaller abnormalities, commercial interests seeking wider markets, the medicalisation of risk and cultural enthusiasm for early detection.[2] Overdiagnosis can also be seen as one aspect of much broader processes of biomedicalization.[8] “In the biomedicalization era” wrote sociologists Clarke and colleagues “what is perhaps most radical is the biomedicalization of health itself”, an era when “it is no longer necessary to manifest symptoms to be considered ill or ‘at risk’”.[8] Armstrong has also described the inexorable rise of “surveillance medicine”, which reconstructs the nature of disease to become “less the illness per se but rather the semi-pathological pre-illness at-risk state.”[9] More recently, in a series in *The BMJ*, researchers are investigating how expanding disease definitions which label more people with milder symptoms or at lower risks are increasing the potential for overdiagnosis, with examples including thyroid cancer,[10], gestational diabetes,[11] and pulmonary embolism.[12]

A 2013 study of the guideline panels which recently changed definitions of 14 common conditions found a majority widened those definitions - including creating pre-hypertension, expanding the diagnosis of myocardial infarction, and lowering diagnostic thresholds for Attention Deficit Hyperactivity Disorder.[13] In addition panel publications did not generally report potential harms of these changes, including risks of overdiagnosis, and among panels which made disclosures, 75% of members had multiple ties to pharmaceutical companies benefiting directly from any increase in populations classified as patients. This finding of extensive conflicts of interest among medical professionals who define human disease is in stark contrast to recommendations from the Institute of Medicine that guideline panels should wherever possible exclude members with conflicts.[14]

While overdiagnosis and expanding disease definitions are recognised as important and related problems, data on public awareness and views about them are extremely limited. In 2004, Schwartz and colleagues found widespread enthusiasm for cancer screening, largely unmodified by awareness of potential harms.[15] More recently Hersch and colleagues published focus group data on Australian women's views on overdiagnosis of breast cancer, finding high enthusiasm for screening and minimal awareness of overdiagnosis, but also a demand for information about the topic.[16] In 2013 an on-line survey of 317 people invited to cancer screening found under 10% were informed by their doctor about the risk of overdiagnosis and overtreatment, and 80% expressed a desire to be informed about these risks.[17] To our knowledge, no previous survey has asked the general community about perceptions and views on overdiagnosis. And while there is data on public views about different aspects of industry-health professional relationships,[18,19] no study has sought community views specifically about ties of panels which change disease definitions.

We aimed to measure the general community's awareness and perceptions about overdiagnosis and views about financial ties of panels which set disease definitions and diagnostic thresholds. Notwithstanding important limitations outlined below, we believe our results will help inform attempts to better communicate about overdiagnosis.

## Methods

We conducted a national Computer Assisted Telephone Interview (CATI) survey with 500 members of the Australian community aged 18 years and older, using a randomly selected dual frame sample - including land-line and mobile phones - during January and February 2014. The survey questionnaire included items about awareness of overdiagnosis, experience of being informed about overdiagnosis during screening, enthusiasm for genetic screening, and attitudes to financial ties of expert panel members who change disease definitions. It also collected demographic information on age, gender, employment, education, and cancer history. Questions were iteratively developed jointly by all authors, based on published and unpublished findings including from focus groups on views about overdiagnosis with 50 women of diverse age and educational background,[16] a qualitative study on patient attitudes,[20] and the 2004 survey of attitudes towards screening.[15]

Draft items were piloted initially by three authors (RM, BN, JH) with a convenience sample of 20 adults. Then 20 pilot telephone interviews were conducted by an experienced social research company, the Social Research Centre, which subsequently conducted 500 interviews.

The survey sample size of 500 was chosen as appropriately powered so that the confidence interval around the proportion responding affirmatively would be approximately 4% either side of the observed proportion for the expected responses to key questions on awareness of overdiagnosis (expected response around 20%), enthusiasm for screening (expected response around 80%), and belief people should be made aware of risks (expected response around 80%).

A dual frame random digit dialling sample design was employed with a 50:50 split between landline and mobile samples. After calling the randomly selected telephone numbers, interviewers asked to speak with the person in the household aged 18 years or over who had the last birthday (landlines) or confirmed if the person answering was over 18 years (mobiles). A slightly modified approach was adopted after approximately 400 interviews, in order to target more difficult to reach demographic groups, notably males and young adults. Rather than asking for the person with the last birthday, the modified screening approach requested to speak with the youngest adult male. Once a potential interview was

established, interviewers provided information about the research purpose and process, and obtained informed consent.(see Ethics Statement below) Answer options included yes/no answers, and Likert type scales to offer more options for intensity of response.

The survey took approximately 15 minutes to complete. Key questionnaire questions and the brief explanation of overdiagnosis offered to participants after the question on unprompted awareness are listed in Box 4. Other questions are available at Appendix 1. An open-ended item and a separate section on concern and treatment preferences relating to ductal carcinoma in situ terminology are being separately analysed and reported elsewhere. At the questionnaire conclusion, participants were asked if they would like to participate in a follow-up qualitative interview about similar topics, and if so, provide name and contact details.

#### Box 4. Survey Questions

| Survey Question                                                                                                                                                                                                                                                                                                                        | Response Format                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <b>On awareness and opinions about overdiagnosis</b>                                                                                                                                                                                                                                                                                   |                                                                        |
| Have you seen or heard the term ‘overdiagnosis’ before today?                                                                                                                                                                                                                                                                          | Yes<br>No<br>Don’t know                                                |
| A generally accepted view is that overdiagnosis happens when people are diagnosed with a disease that would never have harmed them. This could be due to the condition being so slow developing or them displaying only very minor symptoms.<br>Given this explanation, have you seen or heard the term or concept of ‘overdiagnosis’? | Yes<br>No<br>Don’t Know                                                |
| Has a doctor ever told you that healthy people can be over-diagnosed as a result of being screened or tested for a disease?                                                                                                                                                                                                            | Yes<br>No<br>Don’t Know                                                |
| [For those who reported being screened for prostate or breast cancer]: Were you told about the risk of overdiagnosis?                                                                                                                                                                                                                  | Yes<br>No<br>Don’t Know                                                |
| Do you think routine screening tests for healthy people are almost always a good idea?                                                                                                                                                                                                                                                 | Yes<br>No<br>Don’t Know                                                |
| When healthy people are considering having a screening test - along with being told about the potential benefits of the screening test – do you agree or disagree that they should be informed about the potential risk of overdiagnosis?                                                                                              | 7 point Likert scale:<br>Completely Agree<br>to<br>Completely Disagree |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| <b>On enthusiasm for genetic screening</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                      |
| Imagine that there was a genetic screening test which could analyse your genes and identify all the diseases you may ever get, for which some had effective treatments and some did not. Would you be likely or unlikely to have that screening test?                                                                                                                                                                                                                                                                            | 7 point Likert scale:<br>Completely Likely<br>To<br>Completely Unlikely              |
| Imagine now that the results of the genetic screening test were often uncertain, and the predictions could be wrong. Would you be likely or unlikely then to have that screening test?                                                                                                                                                                                                                                                                                                                                           | 7 point Likert scale:<br>Completely Likely<br>To<br>Completely Unlikely              |
| <b>On expert disease panel ties to pharmaceutical companies</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                      |
| From time to time, doctors who specialise in a particular disease will come together to discuss the characteristics of that disease, to decide who should be diagnosed with it and who requires treatment for it. These are called panels and currently some doctors on these panels have financial ties with pharmaceutical companies who market drugs for that disease and some do not.<br>Is it appropriate or inappropriate for doctors who have financial ties with pharmaceutical companies to be members of these panels? | 7 point Likert scale:<br>Completely<br>Appropriate to<br>Completely<br>Inappropriate |
| Ideally, what proportion of the panel should be made up of doctors with financial ties to pharmaceutical companies who market drugs for that disease?                                                                                                                                                                                                                                                                                                                                                                            | None<br>A minority<br>A majority                                                     |

There is debate in the survey literature about different ways to calculate outcome rates, with a key question being to what extent households that could not be contacted or screened are included in the denominator. To assess our sampling strategy we calculated the response rate and cooperation rate as per recommendations and formulae from the American Association for Public Opinion Research.[21] The AAPOR response rate includes in its denominator estimations of the proportion of cases of unknown eligibility which is actually eligible, and calculations involve all households including those where no contact at all was made. The AAPOR cooperation rate excludes un-contacted households, and calculates the proportion of those contacted who cooperated.

No weighting was applied to primary results. For adjusted results, a two-stage weighting process was used where-by a pre-weight to adjust for the overlapping sample was calculated for people with and without a mobile phone. People have varying chances of selection in a dual-frame sample and those with a landline and mobile phone have multiple chances of selection. After these pre-weights were calculated, post-stratification weights were created using rim weighting to adjust weighted proportions to comply with population proportions from four benchmarks obtained from the Australian Bureau of Statistics for gender, age, location and education.[22,23] All results were analyzed descriptively using IBM SPSS Statistics 22, using proportions and confidence intervals. Chi-square tests of association were used to determine the strength of association between demographic variables and four key questions. Variables significant at the 5% level in chi-square analyses were fitted in multivariable models.

### **Ethics Statement**

Ethics approval was granted by the Bond University Human Research Ethics Committee, BUHREC, whose comments helped refine questionnaire text. (Approval #RO1765)

Participants were assured responses would be anonymous and not recorded, and in order to maximise informed consent, a Participant Information Sheet was developed and made available to be read on request, and posted on accessible websites. The information sheet and the process for seeking informed consent were explicitly approved by BUHREC.

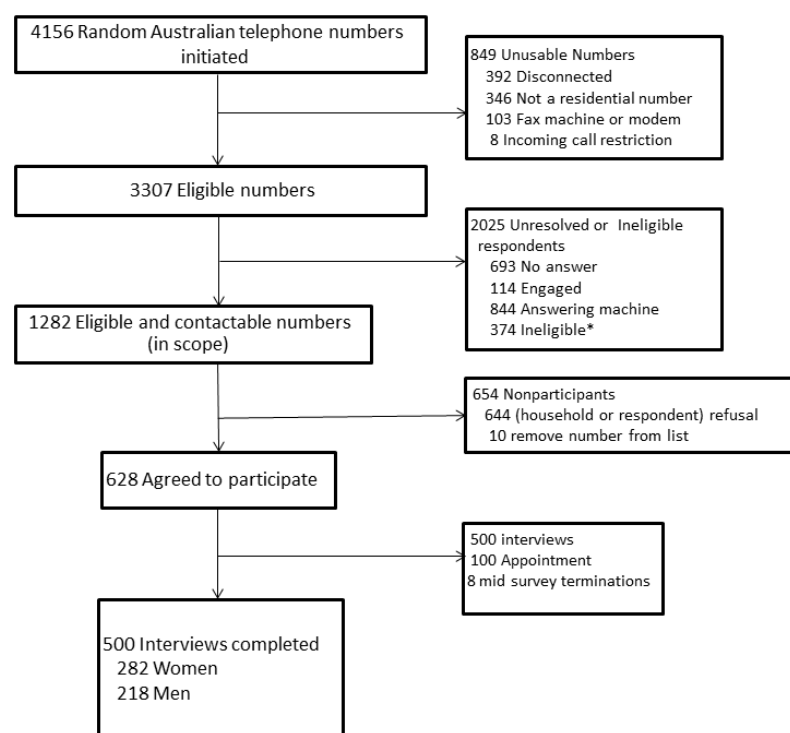
Interviewers underwent a tailored training session in preparation for the survey, covering topics including sensitive subject matter training and strategies for handling distressed respondents.

### **Results**

The random sample selection process commenced with 4,268 numbers available, from which 4,156 landline and mobile calls were initiated, and 3,307 eligible numbers identified. Contact was made with 1,282 numbers from which 500 completed interviews were achieved, 251 from the landline sample and 249 from the mobile phone sample, in addition to the 20 pilot interviews, and 8 mid-survey terminated interviews(Figure 5). The response rate was 20.4% (AAPOR, RR3) and the cooperation rate 43.8% (AAPOR, COOP3).

The sample was generally representative, but included a higher proportion of women and older adults than the general Australian community, as is typical with telephone based health surveys, and slightly higher levels of education (Table 7). All proportions reported here are unadjusted, and both adjusted and unadjusted results are available in Table 8, demonstrating generally minimal impact of adjustment.

**Figure 5. Participant recruitment for Computer Assisted Telephone Interview survey of 500 Australians**



\*Ineligible participants included: persons under age 18 years; those with a medical condition rendering them physically unable to complete the interview; people with language difficulties; respondent away for duration of fieldwork; people claiming to have done survey or named person not known.



**Table 7: Characteristics of survey respondents**

| Characteristic                   | No. of Survey Respondents n=500 (%) |
|----------------------------------|-------------------------------------|
| Age, y                           |                                     |
| 18-29                            | 76 (15.2) *(21.4)                   |
| 30-49                            | 139 (27.8) *(36.5)                  |
| 50-69                            | 209 (41.8) *(29.5)                  |
| ≥70                              | 76 (15.2) *(12.7)                   |
| Sex                              |                                     |
| Men                              | 218 (43.6) *(49.4)                  |
| Women                            | 282 (56.4) *(50.6)                  |
| Education **                     |                                     |
| <High school                     | 74 (14.8) *(26.9)                   |
| High school graduate             | 169 (33.8) *(38.7)                  |
| Bachelor degree/advanced diploma | 168 (33.6) *(26.5)                  |
| >Bachelor degree                 | 89 (17.8) *(7.7)                    |
| Employment                       |                                     |
| Employed                         | 298 (59.6)                          |
| Unemployed                       | 20 (4)                              |
| Not working***                   | 182 (36.4)                          |
| Cancer diagnosis                 |                                     |
| Yes                              | 70 (14.0)                           |
| No                               | 430 (86.0)                          |

\*Australian population data from the Australian Bureau of Statistics 2011 Census; \*\* High school normally completed at age 17;\*\*\* Not in labour force (e.g. student, retired)

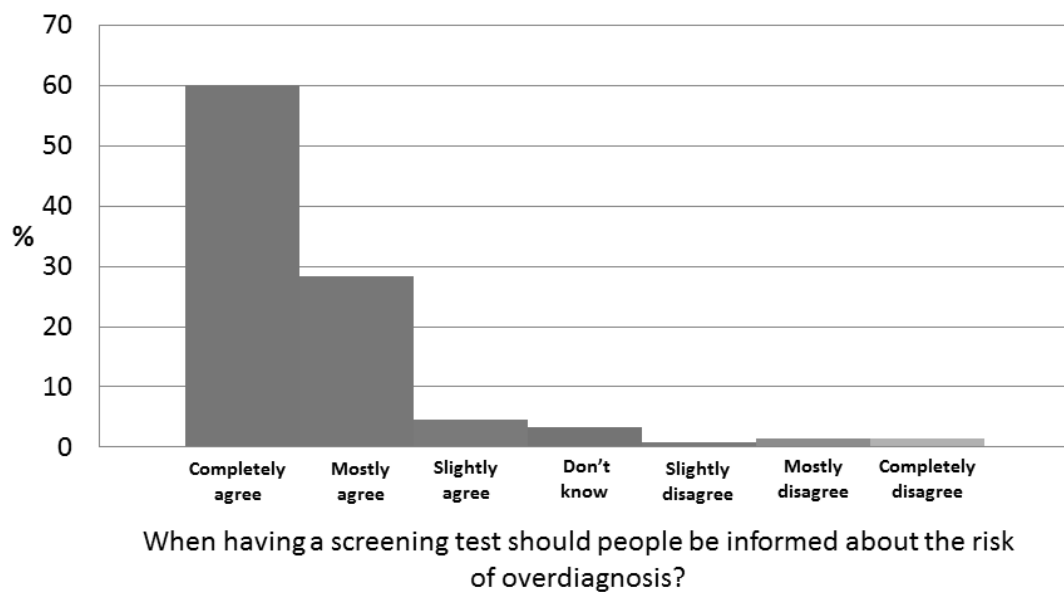
**Table 8: Main results of national community survey on overdiagnosis**

|                                                                                                     | Unadjusted  |             |               |             |                                |             | Adjusted*   |             |               |             |                                |            |
|-----------------------------------------------------------------------------------------------------|-------------|-------------|---------------|-------------|--------------------------------|-------------|-------------|-------------|---------------|-------------|--------------------------------|------------|
|                                                                                                     | Yes/Agree   |             | No/Disagree   |             | Don't know/<br>neither/refused |             | Yes/Agree   |             | No/Disagree   |             | Don't know/<br>neither/refused |            |
|                                                                                                     | n(%)        | (95%CI)     | n(%)          | (95%CI)     | n(%)                           | (95 %CI)    | %           | (95%CI)     | %             | (95%CI)     | %                              | (95% CI)   |
| <b>On overdiagnosis</b>                                                                             |             |             |               |             |                                |             |             |             |               |             |                                |            |
| Seen or heard term 'overdiagnosis' before?                                                          | 313(62.6)   | (58.2-66.8) | 181(36.2)     | (32.0-40.6) | 6(1.2)                         | (0.5-2.7)   | 57.4        | (52.9-61.8) | 41.1          | (36.7-45.4) | 1.5                            | (0.8-3.3)  |
| Doctor ever told you about overdiagnosis?                                                           | 52(10.4)    | (7.9-13.5)  | 443(88.6)     | (85.4-91.2) | 5(1.0)                         | (0.4-2.5)   | 9.7         | (7.2-12.6)  | 89.5          | (86.3-91.9) | 0.8                            | (0.3-2.2)  |
| If screened for prostate cancer, told of overdiagnosis?                                             | 16(18.2)    | (11.1-28.1) | 71(80.7)      | (70.6-88.0) | 1(1.1)                         | (0.1-7.1)   | 15.8        | (9.2-26.3)  | 83.1          | (72.4-89.9) | 1.1                            | (0.1-7.6)  |
| If screened for breast cancer, told of overdiagnosis?                                               | 18(9.7)     | (6.0-15.1)  | 162(87.1)     | (81.2-91.4) | 6(3.2)                         | (1.3-7.2)   | 10.8        | (6.5-17.3)  | 86.4          | (79.5-91.3) | 2.9                            | (0.9-7.3)  |
| Think routine screening almost always good idea?                                                    | 382(76.4)   | (72.4-80.0) | 85(17.0)      | (13.9-20.7) | 33(6.6)                        | (4.7-9.2)   | 79.0        | (75.1-82.4) | 15.1          | (12.1-18.5) | 6.0                            | (4-8.3)    |
| Should people be informed about risk of overdiagnosis?                                              | 465(93.0)   | (90.3-95)   | 18(3.6)       | (2.2-5.7)   | 17(3.4)                        | (2.1-5.5)   | 93.4        | (90.8-95.4) | 3.5           | (2.4-6)     | 3.0                            | (1.9-5.3)  |
| <b>On genetic screening</b>                                                                         |             |             |               |             |                                |             |             |             |               |             |                                |            |
|                                                                                                     | Likely      |             | Unlikely      |             | Don't know/<br>neither         |             | Likely      |             | Unlikely      |             | Don't know/<br>neither         |            |
| Likely or unlikely to have genetic screening test?                                                  | 243(48.6)   | (44.2-53.1) | 226(45.2)     | (40.8-49.7) | 31(6.2)                        | (4.3-8.8)   | 51.0        | (46.5-55.5) | 42.5          | (38.2-47.1) | 6.5                            | (4.7-9.2)  |
| If results uncertain, likely or unlikely to have test?                                              | 142(28.4)   | (24.5-32.6) | 335(67.0)     | (62.7-71.1) | 23(4.6)                        | (3-6.9)     | 31.0        | (27.2-35.5) | 64.0          | (59.6-68.2) | 4.8                            | (3.2-7.2)  |
| <b>On financial ties of disease-defining panels</b>                                                 |             |             |               |             |                                |             |             |             |               |             |                                |            |
|                                                                                                     | Appropriate |             | Inappropriate |             | Don't know/<br>neither/refused |             | Appropriate |             | Inappropriate |             | Don't know/<br>neither/refused |            |
| Appropriate or inappropriate for doctors with ties to pharmaceutical companies to be panel members? | 71(14.2)    | (11.3-17.6) | 391(78.2)     | (74.3-81.7) | 38(7.6)                        | (5.5 -10.4) | 16.2        | (13-19.6)   | 75.6          | (71.6-79.3) | 8.1                            | (5.8-10.8) |

\*Adjustment involved two-step, rim weighting as described in Methods; due to rounding some rows do not add to 100%; calculation of Confidence Intervals includes continuity correction

Of all participants, 63% (95% CI 58%-67%) said they had heard or seen the word overdiagnosis before, although following a brief explanation of the term to all participants (Box 4) the number fell to 50% (95% CI 45%-54%). Only 10% of people said they had ever been told by a doctor that overdiagnosis was a risk of being screened or tested, (95% CI 8%-13%). Only 18% of men who reported having had prostate cancer screening (95% CI 11%-28%) and 10% of women who reported having had a mammogram (95% CI 6%-15%) said they were told about the risk of overdiagnosis. 76 % of participants (95% CI 72%-80%) agreed screening tests were almost always a good idea and 93% (95% CI 90%-95%) agreed (88% completely or mostly agreed) that along with the benefits of screening, people should be informed about the risk of overdiagnosis(Figure 6).

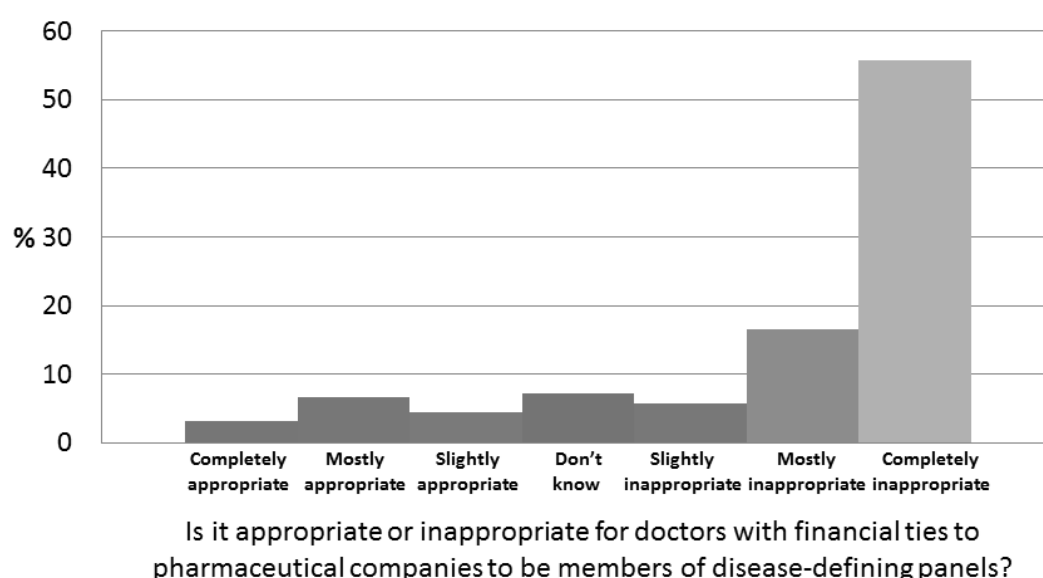
**Figure 6. Community views about availability of information on overdiagnosis**



Asked about enthusiasm for a genetic screening test, the community was split almost equally, with 49% likely to have a screening test, (95% CI 44%-53%) and 45% unlikely, (95% CI 41%-50%). When asked to imagine the results of genetic screening tests were often uncertain and predictions potentially wrong, enthusiasm waned dramatically, with 28% likely, (95% CI 25%-33%) and 67% unlikely, (95% CI 63%-71%) to undergo tests.

In response to questions about panels which set disease definitions, 78% (95% CI 74%-82%) felt it inappropriate (72% completely or mostly inappropriate) for members to have financial ties to pharmaceutical companies (Figure 7). Asked what proportion of panel members would ideally have financial ties to pharmaceutical companies, 55% (95% CI 50%-59%) said there should be no panel members with ties, 36% (95% CI 32%-40%) said a minority - less than 50%, and 5% (95% CI 3%-7%) said a majority - 50% or more. At the conclusion of the survey, 81% of all participants volunteered to take part in a qualitative follow-up study. The number of refusals to answer questions was negligible.

**Figure 7. Community views about financial ties of panel members who set disease definitions**



For four key questions - unprompted awareness of overdiagnosis, whether participants had been informed about overdiagnosis, merits of routine information about overdiagnosis, and appropriateness of financial ties for disease panels - we looked for associations with 5 key demographics: age, gender, employment, education and cancer history. For gender and employment, we found no significant associations. Responses to unprompted awareness of the term overdiagnosis had significant associations with age, education status and cancer history. After re-coding multiple categories for age into two categories above and below the

median age, and removing “don’t knows” and refusals, among those aged 53 and younger, 57% said yes they had heard or seen the term, while for those older than 53 years, 71% said yes, (chi-square 9.7,  $p=0.002$ ). For those with a history of cancer, 76% said yes they had heard or seen the term, and for those without 61% said yes (chi-square 5.5,  $p=0.019$ ). After re-coding the highest level of education into two categories, among those with education up to and including year 12 (~age 17), 51% said they were aware of the term, while for those with a post-year 12 education the figure was 68%, (chi-square 12,  $p=0.001$ ). The only other significant association also involved education levels: those with higher levels were slightly more likely to report a doctor had informed them about overdiagnosis (13% vs 6%; chi square 5.0,  $p=0.025$ ).

The only key outcome that had more than one significant association with a demographic variable was the question about having heard of the term ‘overdiagnosis’. Therefore, age (above and below the median age), educational level (above and equal to or below year 12 attainment) and history of cancer diagnosis were used as predictors in multivariable logistic regression. All were significant. The adjusted odds ratio for reporting having heard of overdiagnosis was 1.8 for the older age group ( $p=0.003$ , 95% CI 1.2 to 2.7), 2.2 for educational level above year 12 ( $p=0.001$ , 95% CI 1.5 to 3.4) and 1.9 for those with a history of cancer diagnosis ( $p=0.048$ , 95% CI 1.0 to 3.4).

## Discussion

Our community survey found a large majority of adults reporting they had not been informed about the risk of overdiagnosis attached to screening tests, and a large majority expressing the view that along with screening benefits, people should be informed of the risk of overdiagnosis. Despite strong evidence overdiagnosis is a significant risk of prostate cancer screening,[6] 81% of men who reported being screened said they had not been told; among women who reported having breast cancer screening, where overdiagnosis is also now an established risk,[5] 87% said they hadn’t been informed. A third of respondents said they had not seen or heard of the term before, with those who were older, more highly educated and with a history of cancer more likely to say they had.

Over two-thirds of Australians surveyed felt it was completely or mostly inappropriate for doctors with financial ties to pharmaceutical companies to serve on panels which set disease definitions. Moreover, when asked how these panels should ideally be constituted, just over half of all participants said they should have no doctors with financial ties.

Against a background of concern widespread promotion of genetic screening could produce new vectors for overdiagnosis,[24] we found public enthusiasm might be modified if people were informed the results of screening tests could be uncertain or potentially wrong. Given the propensity of media coverage to over-promote benefits and minimise harms,[25] our findings suggest routine provision of information about the limitations and potential harms of screening tests may be desirable.

Our study has several important limitations. As part of the survey methodology we axiomatically relied solely on unverified self-reports. While previous data suggests telephone survey self-reports of screening are reliable indicators of actual behaviour,[26] some of the large majority who reported not being informed about overdiagnosis may in fact have been informed. Secondly, because this is a new area of inquiry, our questionnaire has not been used before, apart from the question on enthusiasm for screening taken with minor modification from a previously published national survey.[15] While new items were rigorously piloted by the research team and social research company using a multi-stage pilot process with 40 adults, and explicit efforts were made to ensure questions were not leading, we cannot exclude the possibility some responses may be influenced by the questions. A third limitation arises from the complexity of the material, though there was a strong focus on comprehensibility and clarity in questionnaire development and interviewer training.

A final limitation arises from the AAPOR response rate of 20.4% and cooperation rate of 43.8%. While modest, these rates are common and considered satisfactory for community surveys of this type. In 2012 the highly regarded Pew Research Centre stated its standard telephone surveys were achieving an AAPOR response rate of 9%, and cooperation rate of 14%, and that the 9% response rate was similar to that achieved by other major survey organisations.[27] With the outcome rates achieved there is a possibility of systematically

different responses between respondents and non-respondents, though this possibility is lessened by the general representativeness of sample respondents.

Alongside limitations, the study has important strengths. In the context of growing evidence about overdiagnosis this is to our knowledge the first national telephone survey to assess how the general community reports being informed about the topic, finding both a deficit of information and a desire for it. Secondly, we gathered rare and novel data on community attitudes about the timely question of who should most appropriately be setting diagnostic criteria which determine the nature and extent of human pathology. And finally, our random sample was generally representative of the Australian community, achieved in part as a result of our dual frame method, reaching both landline-users and the fast growing demographic of mobile-only users, now estimated to be more than 20% of phone users in Australia,[28] and 38% in the United States.[29] Moreover, generally negligible differences between adjusted and unadjusted results strengthen representativeness and generalizability, and potential applicability to other nations with similar demographics.

There is extremely limited data on public awareness about overdiagnosis. A small on-line survey limited to individuals who had been invited to undergo cancer screening - reported briefly as a research letter in 2013 - found only 9.5% reported they'd been informed by a physician about the risk of overdiagnosis and overtreatment, and 80% felt people should be routinely informed of such screening harms.[17] Similarly our survey found only 10% of women who reported undergoing breast screening said they were told of these harms, and just 18% of men who reported having prostate screening, while 88% completely or mostly agreed people should be informed about the risk of overdiagnosis, echoing findings from a 2002 survey of around 650 Australian women, which found over 90% wanted to receive information about false results or mammogram side effects[30]. This strong community desire for information about harms is set against a backdrop of widespread enthusiasm for screening. In 2004 Schwartz and colleagues found 87% agreed routine cancer screening was almost always a good idea,[15] while 76% agreed with a similar proposition in our survey a decade later.

There are mixed findings on public attitudes to financial ties between health professionals and industry. Some studies suggest trial participants want information about investigator

financial ties, but are not deterred by them,[18] while other studies find concern is strongest where the tie brings direct benefits, such as the professional being paid research recruitment fees.[19] To our knowledge, no previous study has investigated public opinions about the pharmaceutical company ties of panels which set disease definitions. Our findings of strong public antipathy to these ties is significant and timely: in tune with Institute of Medicine recommendations to minimise and eliminate them,[14] but in contrast to current reality, where many panel members have such ties.[13]

In light of the limitations of this telephone survey, and the complexity of the material covered, caution in interpretation is appropriate. In 2014 researchers in the United Kingdom reported that even written information about overdiagnosis and mammography was not well understood.[31] However, despite the complexity, at the completion of our survey, around 400 of the 500 participants, ultimately shared personal details and agreed to take part in a follow-up qualitative research project, underscoring not only a positive survey experience, but suggesting a public hunger to learn more about overdiagnosis and related issues. While increasing numbers of research projects are underway worldwide investigating the nature and extent of overdiagnosis, these findings, notwithstanding limitations, point to the need to find ways to better communicate with the community about the problem. Not least to facilitate more informed decision making, but more broadly, as Clarke suggests,[8] to enable “greater democratic participation” in shaping the future of relationships between people and their health care.

### **Acknowledgements**

We would like to thank Paul Glasziou and Chrissy Erueti at the Centre for Research in Evidence-Based Practice,(CREBP) Faculty of Health Sciences and Medicine, Bond University for on-going support and assistance, Evelyne Rathbone at CREBP for statistical assistance, members of the Bond University Human Research Ethics Committee for their input into the survey, and staff at the Social Research Centre involved in developing and running the survey. We are deeply grateful to all survey participants for volunteering their time for this research.



**Author contributions**

RM, KM and JD obtained study funding. RM initiated the idea for the survey. RM, BN, JH, EB, JD, SC, AB, LB and KM developed and designed the survey questionnaire, in liaison with staff at the Social Research Centre. RM developed and wrote the first draft of the manuscript and managed subsequent iterations, and all authors critically reviewed the manuscript and contributed to revisions before submission. (The manuscript version here is the version submitted to PLOS ONE. The final published manuscript is not available at time of finalising revisions to the PhD.)

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## **Chapter 6 What do you think overdiagnosis means?: a qualitative analysis of responses from a national community survey of Australians**

**In Press, *BMJ Open*, 2015**

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## Abstract

### Objective

Against a backdrop of growing evidence and concern about the risk of overdiagnosis associated with some screening activities, and recognition of the need to better inform the public about it, we aimed to ask what the Australian community understood overdiagnosis to mean.

### Design, setting and participants

Content analysis of verbatim responses from a randomly sampled community survey of 500 Australian adults, between January and February 2014. Data were analysed independently by two researchers.

### Main Outcome Measures

Analysis of themes arising from community responses to open-ended questions about the meaning of overdiagnosis.

### Results

The sample was broadly representative of the Australian population. The American Association for Public Opinion Research response rate was 20% and cooperation rate, 44%. 40% of respondents thought overdiagnosis meant exaggerating a condition that was there, diagnosing something that was not there, or too much diagnosis. 24% described overdiagnosis as overprescribing, overtesting, or overtreatment. Only 3% considered overdiagnosis meant doctors gained financially. No respondents mentioned screening in conjunction with overdiagnosis, and over 10% of people were unable to give an answer.

### Conclusions

Around half the community surveyed had an approximate understanding of overdiagnosis, although no-one identified it as a screening risk and a quarter equated it with overuse. Strategies to inform people about the risk of overdiagnosis associated with screening and other diagnostic tests, in clinical and public health settings, could build on a nascent understanding of the nature of the problem.

**Strengths and limitations of this study**

- This is the first study to ask the general community about the meaning of overdiagnosis, a problem attracting growing research attention
- Our survey sample was generally representative of the Australian community
- Findings offer a unique and rich dataset of public understanding, to help inform strategies to communicate better about overdiagnosis and overuse
- Limitations arise from the modest response and cooperation rates, though similar rates are now common with telephone surveys
- Another limitation arises because survey participants had little time to reflect on the meaning of overdiagnosis before responding

**Introduction**

Overdiagnosis occurs when a person is diagnosed with a disease that would not have harmed them, and evidence is emerging the problem is associated with a range of conditions.[1] There are a number of drivers of overdiagnosis including the medicalization of risk,[2] improvements in diagnostic technology which identify ever-smaller “abnormalities”, widening disease definitions, and cultural enthusiasm for early detection.[3] Appearing in the medical literature as early as the 1970s, the complex and counter-intuitive concept is attracting increasing research attention, as part of wider interest in preventing avoidable medical excess, manifested in initiatives including *JAMA Internal Medicine’s* Less is More,[4] *Choosing Wisely*, [5] and *The BMJ’s* Too Much Medicine series on expanding disease definitions and the risk of overdiagnosis.[6] To our knowledge however there are no data on what the community understands overdiagnosis to mean.

While scientific debate about the nature and extent of overdiagnosis continues, evidence is most well advanced in the field of cancer screening. After assessing all available evidence, an independent panel in 2012 estimated 19% of breast cancers detected during mammography screening may be overdiagnosed: defined as detection of cancers that don’t progress to be symptomatic and “would never have been found were it not for the screening test.”[7] In the same year the United States Preventive Services Task Force pointed to

“convincing evidence that PSA-based screening leads to substantial overdiagnosis of prostate tumors”, with estimates ranging from 17% to 50%.[8]

This evidence has contributed to recognition of the need for greater professional and public awareness of the problem. In 2013 a working group convened under the auspices of the United States National Cancer Institute stated, “Physicians, patients, and the general public must recognize that overdiagnosis is common and occurs more frequently with cancer screening.”[9] In late 2014, the science and technology committee of the United Kingdom parliament produced a report calling for routine communication of the benefits and risks of screening programs.[10] In November 2014, a report from the Academy of Medical Royal Colleges signalled a “cultural shift” away from unnecessary medical care,[11] underscoring the need for new clinical approaches including “de-prescribing” strategies designed to confront inappropriate poly-pharmacy.[12] In order to inform on-going scientific and policy debates about how to effectively communicate about overdiagnosis and related overuse in clinical and public health settings, we aimed to discover what the community currently understood overdiagnosis to mean.

## **Methods**

We conducted a Computer Assisted Telephone Interview (CATI) survey of randomly selected adult Australians to explore understanding of overdiagnosis. The survey recruited 500 Australians aged 18 years and older using a randomly selected dual frame sample, including landlines and mobile phones. As per formulae from the American Association for Public Opinion Research (AAPOR),[13] we calculated the AAPOR response rate - which includes in its denominator estimations of the proportion of cases of unknown eligibility which is actually eligible, and calculations involve all households including those where no contact at all was made - and the AAPOR cooperation rate - which excludes un-contacted households, and calculates the proportion of those contacted who cooperated.

A survey questionnaire was developed iteratively and piloted with a convenience sample of 20 adult Australians and then through an experienced social research company, The Social Research Centre, with an additional 20 recruited participants. Ethics approval was granted by the Bond University Human Research Ethics Committee, BUHREC, (Approval #RO1765).

Participants were assured responses would be anonymous and not recorded, and in order to maximise informed consent, a Participant Information Sheet was developed and made available to be read on request, and posted on accessible websites. The information sheet and the process for seeking informed consent were explicitly approved by BUHREC. The final CATI survey lasted for an average of 15 minutes and was conducted by The Social Research Centre between January and February 2014.

Following an initial question asking “Have you seen or heard the term ‘overdiagnosis’ before today?”, participants who said yes were then asked “What do you understand the term overdiagnosis to mean?” and if they said no or “don’t know” they were asked, “What do you think the term ‘overdiagnosis’ means?” Responses were transcribed verbatim. Quantitative elements of the survey are being analysed and reported separately from this qualitative analysis of participants’ verbatim responses.

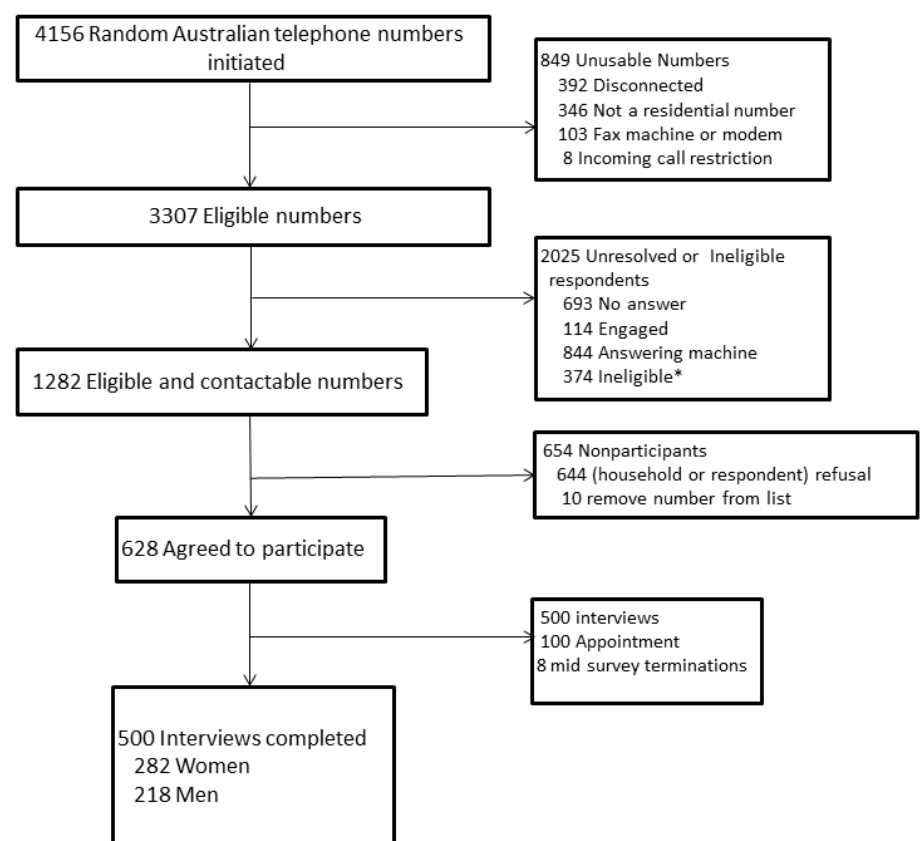
Upon completion of the survey, we used content analysis of the verbatim responses to identify and code emergent themes that captured the diverse understanding of overdiagnosis.[14] Two authors (RM, BN) independently reviewed the verbatim responses from the 500 participants, and identified salient themes. To ensure rigour of the analysis, we used constant comparison methods,[15,16] to look for similarities and differences in the themes across responses. The two sets of independently identified major themes were documented and discussed with co-authors (JD, JH, KM, AB) and an initial coding framework of themes was developed and then pilot tested, by independent double coding of 50 of the verbatim responses by RM and BN. By comparing and reviewing the pilot data, and with more discussion with the experienced qualitative researcher on our research team (KM), the final coding framework was then developed. For final coding, the 500 verbatim responses were randomized, and two authors (RM, BN) independently coded 300 responses each, including 100 responses which were double coded, resulting in agreement in over 80% of cases in assigning responses to themes. A single response could be coded to more than one theme.



## Results

Of 4,156 landline and mobile calls initiated, 3,307 eligible numbers were identified and contact made with 1,282 numbers from which 500 completed interviews, plus 20 pilots, were achieved. (Figure 5) The response rate was 20.4% (AAPOR, RR3) and the cooperation rate (people who completed the survey, as a proportion of those who completed, plus those who refused) 43.8% (AAPOR, COOP3). The sample was generally representative, but included a higher proportion of women and older adults than the general Australian community, as is typical with telephone based health surveys, and slightly higher levels of education (Table 7).

**Figure 5. Participant recruitment for Computer Assisted Telephone Interview survey of 500 Australians**



\*Ineligible participants included: persons under age 18 years; those with a medical condition rendering them physically unable to complete the interview; people with language difficulties; respondent away for duration of fieldwork; people claiming to have done survey or named person not known

**Table 7: Characteristics of survey respondents**

| Characteristic                   | No. of Survey Respondents n=500 (%) |
|----------------------------------|-------------------------------------|
| Age, y                           |                                     |
| 18-29                            | 76 (15.2) *(21.4)                   |
| 30-49                            | 139 (27.8) *(36.5)                  |
| 50-69                            | 209 (41.8) *(29.5)                  |
| ≥70                              | 76 (15.2) *(12.7)                   |
| Sex                              |                                     |
| Men                              | 218 (43.6) *(49.4)                  |
| Women                            | 282 (56.4) *(50.6)                  |
| Education                        |                                     |
| <High school                     | 74 (14.8) *(26.9)                   |
| High school graduate             | 169 (33.8) *(38.7)                  |
| Bachelor degree/advanced diploma | 168 (33.6) *(26.5)                  |
| >Bachelor degree                 | 89 (17.8) *(7.7)                    |
| Employment                       |                                     |
| Employed                         | 298 (59.6)                          |
| Unemployed                       | 20 (4)                              |
| Not working                      | 182 (36.4)                          |
| Cancer diagnosis                 |                                     |
| Yes                              | 70 (14.0)                           |
| No                               | 430 (86.0)                          |

\*Australian population data from the Australian Bureau of Statistics 2011 Census

Of 500 participants, 433 offered a response to the question about the meaning of the term overdiagnosis. After independent content analysis of themes by RM and BN, for 9 major themes there was clear agreement between the two authors on the nature of the theme. Following discussion with co-authors, and piloting of the coding framework, a final list of 10 themes were agreed upon. Following independent double coding of 100 responses, in 82 cases there was agreement on the theme/s a response was coded to, including 5 cases where one or other coder assigned the response to an additional theme as well. All discrepancies were resolved by discussion.

The final ten themes and their accompanying explanations are listed in Table 9. These ten themes were then divided into three categories described as: 1) approximate understanding of overdiagnosis; 2) overuse; and 3) other. The most prevalent theme of the responses was “exaggerating something that is there”, which included responses suggesting overdiagnosis

meant “diagnosing a condition to be more serious/severe than what it actually is; overmedicalising; overcomplicating.” 22% of responses were coded as fitting into this theme, exemplified by the comment, *“Someone’s condition has been made out to be worse than what it is.”* (Table 10) Responses in this theme revolved around ideas that diagnostic labels made problems seem more severe than what they were, causing unnecessary fear or worry. (see more examples of all themes in Table 11) Another example of a comment in this theme was: *“When a patient presents with symptoms and the doctor diagnoses it as something more serious than it is, for example, when a boisterous child is diagnosed with ADHD when they just have a lot of energy.”* ADHD was the most commonly mentioned condition, appearing in 8 responses.

**Table 9: Coding framework for analysis of responses to “What do you think overdiagnosis means?”**

| Theme                                  | Explanation of theme                                                                                                           |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| <i>Overdiagnosis</i>                   |                                                                                                                                |
| Exaggerating something that is there   | diagnosing a condition to be more serious/severe than what it actually is; overmedicalising; overcomplicating                  |
| Diagnosing something that is not there | diagnosing a condition that the person does not actually have/does not exist                                                   |
| Too much diagnosis/too many diagnoses  | doctors making a diagnosis more frequently than what is needed/people being diagnosed with too many conditions                 |
| <i>Overuse</i>                         |                                                                                                                                |
| Overprescribing                        | prescribing too many medications - more than is needed                                                                         |
| Overtreatment                          | unnecessary medical interventions and services provided, including referrals; overservicing                                    |
| Overtesting                            | a doctor performing or a person having too many unnecessary tests to get a diagnosis                                           |
| <i>Others</i>                          |                                                                                                                                |
| Doctors looking too much into things   | doctors looking too hard, too much or too often for a problem to diagnose                                                      |
| Patients/people driving it             | patients/people who search for too much unnecessary medical information or are unusually anxious or worried about their health |
| Wrong diagnosis                        | wrongly diagnosed with a condition (with no suggestion of exaggerating something)                                              |
| Doctors financial gain as a driver     | doctors whose ultimate goal is to make money or cover themselves for financial or litigation reasons                           |

**Table 10: What do you think overdiagnosis means?: response theme, example, and frequency**

| Theme                               | Example of comment                                                                                                                    | Number | (% of 500)* |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--------|-------------|
| <i>Overdiagnosis</i>                |                                                                                                                                       |        |             |
| Exaggerating something that's there | Someone's condition has been made out to be worse than what it is                                                                     | 112    | 22          |
| Diagnosing something not there      | Sort of pre-empting a potential disease when there isn't one                                                                          | 48     | 10          |
| Too much/too many diagnoses         | I take it to mean something like ADHD, where previously it hadn't been diagnosed and now it is and suddenly people find it everywhere | 45     | 9           |
| <i>Overuse</i>                      |                                                                                                                                       |        |             |
| Overprescribing                     | A doctor is handing out medication willy nilly                                                                                        | 69     | 14          |
| Overtreatment                       | Over servicing or providing greater service than is essential for the correct diagnosis                                               | 26     | 5           |
| Overtesting                         | Where too many tests are done, particularly with prostate cancer                                                                      | 33     | 7           |
| <i>Others</i>                       |                                                                                                                                       |        |             |
| Doctors looking too much            | Looking too far into a problem                                                                                                        | 21     | 4           |
| Patients driving it                 | People get on the internet and diagnosing themselves with things they don't have                                                      | 22     | 4           |
| Wrong diagnosis                     | That they haven't diagnosed you correctly or they have given you the wrong diagnosis                                                  | 20     | 4           |
| Doctors' financial gain             | They want to make more cost for patients and make more money or they sometimes go further to cover themselves.                        | 17     | 3           |
| <i>Non-responses</i>                |                                                                                                                                       |        |             |
| Did not respond at all              |                                                                                                                                       | 67     | 13          |
| Miscellaneous/don't know/unsure     |                                                                                                                                       | 61     | 12          |

\*does not add to 100% as some responses coded to more than 1 theme

**Table 11. What do you think overdiagnosis means? Additional examples of responses****Exaggerating something that is there**

I'm guessing it means a mountain made out of a mole hill

Making diseases more severe than they are

When a patient presents with symptoms and the doctor diagnoses it as something more serious than it is, for example, when a boisterous child is diagnosed with ADHD when they just have a lot of energy

Someone's condition has been made out to be worse than what it is

Maybe reading too much into symptoms

Something that's not really serious making it sound as though it is really bad

They over diagnose what's going on with a person and they scare them more than they need to

It might mean that they've given a diagnosis that you're far worse off than you really are

When you're diagnosed with something but it's not as life threatening as its being explained to be

**Diagnosing something that is not there**

When they assign diseases to people who aren't ill.

Diagnosing a disease some one doesn't have.

Doctor seeing things that aren't there.

There is so many different ailments around and now there are so many different medications now it's possible that doctors are describing things that aren't there.

**Too much diagnosis/too many diagnoses**

When there are more people given a label than you would expect to be the case

For example cholesterol, they just use a level in the blood and if you are over the level you have that and they lower the level so everyone has it.

I take it to mean something like ADHD, where previously it hadn't been diagnosed and now it is and suddenly people find it everywhere

**Overprescribing**

Too much medication.

Doctors trying to give out drugs that don't need to be taken to cure an ailment.

You are being given too much medication when you don't need it.

**Overtreatment**

If you have an illness where there are too many treatments for it.

Over servicing of a patient's needs.

**Overtesting**

---

Doctors sending people for too many tests.

I think they send you off to have this test or that test and it's all a bit unnecessary.

---

**Doctors looking too much**

When a doctor is looking for too many things.

---

**Patients driving it**

If you go on the internet and you're looking at things you're just taking the information but it's probably the wrong information.

---

**Wrong diagnosis**

The doctor wrongly diagnoses.

---

**Doctors' gain**

Generally speaking it's a doctor who is milking the system to get more funds.

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Related to the “exaggeration” theme was the theme described as “diagnosing something not there”, which included responses which defined overdiagnosis as “diagnosing a condition that the person does not actually have/does not exist” and exemplified by the comment *“Sort of pre-empting a potential disease when there isn’t one.”* This theme occurred in 10% of responses. Also related was the theme “too much or too many diagnoses”, explained as “doctors making a diagnosis more frequently than what is needed/people being diagnosed with too many conditions”. This theme was exemplified by the response, *“For example cholesterol, they just use a level in the blood and if you are over the level you have that and they lower the level so everyone has it”*, and this occurred in 9 % of responses. While none of the three related themes corresponds exactly with the current definitions of overdiagnosis being debated within the scientific community, they can be seen to approximate an understanding of the problem of an unnecessary and unhelpful diagnosis.

The second most common set of themes related to overuse of interventions, occurring in 24% of responses. The theme of “overprescribing” - which was described as “prescribing too many medications/more than is needed” - ran through 14% of responses, exemplified by the comment, *“A doctor is handing out medication willy nilly.”* This theme related closely to “overtreatment” - defined as “unnecessary medical interventions and services provided, including referrals; overservicing.” The overtreatment theme was exemplified by the comment, *“Over servicing or providing greater service than is essential for the correct diagnosis”* and occurred in 5% of responses. The theme “overtesting” - defined as “a doctor performing or a person having too many unnecessary tests to get a diagnosis” - was exemplified by the comment *“Where too many tests are done, particularly with prostate cancer”* and occurred in 7% of responses.

Relatively small numbers of people made responses coded into themes including “doctors looking too much”,(4%) “patients driving it”,(4%) “wrong diagnosis”,(4%) and “doctors’ financial gain.”(3%) Around 13% of participants failed to respond, and for another 12% their responses were unable to be categorised into the final 10 themes, because for example a participant answered by saying *“probably overdiagnosis”*. No responses mentioned screening.



## Discussion

Our survey of 500 Australian adults found almost half of participants thought the term overdiagnosis meant exaggerating a problem that exists, diagnosing something that is not there, or deploying too many diagnoses, and another quarter equate the term with some form of overuse, including overprescribing, overtesting or overtreating. A significant minority offered either no response, or a response unable to be categorised. Only a tiny proportion gave responses which made mention of doctors' financial gain, and notably no respondent mentioned the association between overdiagnosis and screening.

This study has several limitations. First, the brevity of some participant responses made coding into themes more difficult for answers where comprehensibility was in doubt and roughly one in ten responses were unable to be categorised into our final 10 themes. Second, the open-ended question to participants about the meaning of overdiagnosis happened at the very start of the survey, enabling valuable analysis of unprompted understanding of the term, but not giving participants much time to reflect or think through responses. A third limitation arises from the AAPOR response rate of 20.4% and cooperation rate of 43.8%. While modest, these rates are however now common and satisfactory for community surveys of this type. In 2012 the well regarded Pew Research Centre stated its standard telephone surveys were achieving AAPOR response rates of 9%, and cooperation rates of 14%, and that the 9% response rate was similar to that achieved by other major survey organisations.[17] With the rates achieved in our survey there is a possibility of systematically different responses between respondents and non-respondents, though this possibility is lessened by the general representativeness of sample respondents.

Study strengths include the strong level of agreement on themes in the initial independent coding of the 500 responses, pointing to a thematic coherence in the community's response, and notwithstanding demographic variations between our random sample and population data, the study's 500 Australian adults were generally representative. Most importantly, to our knowledge this is the first time internationally that general community members have been asked what they understand overdiagnosis to mean, with responses providing a unique dataset. Other data on public understanding or views about overdiagnosis are extremely limited. A quantitative survey by Schwartz and colleagues in 2004 found

widespread enthusiasm for screening, unmodified by awareness of potential harms,[18] while a qualitative study published in 2013 involving focus groups with 50 Australian women aged 40-79 found few had heard of overdiagnosis, though there was a desire to know more.[19] In 2014 researchers found brief written information about overdiagnosis and mammography, of the sort currently sent to women in the United Kingdom, was incompletely understood and may not be enough to facilitate informed choice.[20]

At a time when the scientific community is still debating the definition of overdiagnosis, it makes little sense to judge the accuracy of community comprehension. Instead, we interpret the results to suggest that while many people grasp the basic idea overdiagnosis means too many unnecessary diagnoses, many others failed to offer even an approximate understanding. For clinicians attempting to explain to their patients the counter-intuitive concepts like the risk of overdiagnosis or the value of choosing not to test or to reduce or stop medication for instance,[11,12] our results point to an encouraging though limited reservoir of community recognition of the potential dangers of excess. Clinicians may also take heart from how very few respondents identified doctors' financial gain as relevant to the meaning of overdiagnosis. Our finding that almost one in four respondents associated overdiagnosis with overuse suggest overdiagnosis might be best communicated about not in isolation, but within a wider context of its potential harms, including overuse. And finally, we believe the failure to associate overdiagnosis with screening should be interpreted as a strong signal to policy-makers to introduce more routine communication about potential benefits and harms into screening programs.

While there are ongoing and complex debates about how to define and measure overdiagnosis, and resulting disagreements over its magnitude and extent, there is a growing consensus around the need to communicate better with the community about the problem, particularly as a risk of screening. Our findings offer a rich dataset of lay understanding to researchers and policy makers, to help inform development of effective communication strategies. Notwithstanding the complexity of the issues, the community responses provide some refreshingly simple and clear insights - such as suggesting the meaning of overdiagnosis might be akin to "*a mountain made out of a molehill*" - reinforcing

the need to intimately involve community members in developing and evaluating future communication strategies.

**Acknowledgement**

We would like to thank Chrissy Erueti at the Centre for Research in Evidence-Based Practice,(CREBP) Faculty of Health Sciences and Medicine, Bond University for on-going support and assistance, members of the Bond University Human Research Ethics Committee for their input into survey, and staff at The Social Research Centre, including Shane Compton, who were involved in developing and running the survey. We are deeply grateful to all survey participants for volunteering their time for this research. (The manuscript version here is the version submitted to BMJ Open. The final published manuscript is not available at time of finalising revisions to the PhD.)

**Author Contributions**

RM initiated the idea for the survey and for this analysis. RM, KM and JD obtained study funding. RM, BN, JH, EB, JD,AB, KM designed the survey. RM and BN analysed the responses to the survey question about the meaning of overdiagnosis. RM developed and wrote the first draft of the manuscript, and all authors critically reviewed it and contributed to revisions before submission. KM supervised all aspects of this study.

**Competing Interests**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: RM and JD positions receive funding from the Screening and Test Evaluation Program (STEP) grant from the National Health and Medical Research Council, NHMRC, #633003; the survey received part funding from a Bond University Vice-Chancellors Research Grant and part funding from NHRMC (STEP) grant #633003; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; RM, JD and AB are members of the steering committee which helped organise the 2013 and 2014 Preventing Overdiagnosis conferences.

**Funding**

RM and JD positions receive funding from Screening and Test Evaluation Program (STEP) grant from the National Health and Medical Research Council ([www.nhmrc.gov.au](http://www.nhmrc.gov.au)) (NHMRC) #633003; EB's position receives funding from Australia Fellowship grant: Glasziou NHMRC #527500; the survey received part funding from a Bond University Vice-Chancellors Research Grant ([www.bond.edu.au](http://www.bond.edu.au)) and part funding from NHRMC (STEP) grant #633003. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### **Transparency Declaration**

Ray Moynihan, lead author, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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## **Chapter 7 Using Evidence to Combat Overdiagnosis and Overtreatment: Evaluating Treatments, Tests, and Disease Definitions in the Time of Too Much**

*PLoS Med* 2014;11(7):e1001655.

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## Summary Points

- Overdiagnosis and related overtreatment are increasingly recognised as major problems.
- “Positive” average results from trials of treatments can mask situations where many participants at low risk of disease may receive no benefit.
- The evaluation of diagnostic tests usually involves assessing how well tests detect presence versus absence of a certain disease—rather than how well they detect clinically meaningful stages of disease.
- Changes to disease definitions typically do not involve evaluation of potential harms of overdiagnosis, and are often conducted by heavily conflicted panels.
- We offer suggestions for improving the way evidence is produced, analysed, and interpreted, to help combat overdiagnosis and related overtreatment. These include routine consideration of overdiagnosis and related overtreatment in studies of tests and treatments, and clearer stratification by baseline risk to identify treatment thresholds where benefits are likely to outweigh harms.

While a large part of the world's population faces the problems of underdiagnosis and undertreatment, it is apparent that a “modern epidemic” of overdiagnosis afflicts high-income countries,[1] with tangible human and financial costs of the unnecessary management of overdiagnosed diseases.[2,3] While there is ongoing debate about how to best describe the problem, narrowly defined, overdiagnosis occurs when increasingly sensitive tests identify abnormalities that are indolent, non-progressive, or regressive and that, if left untreated, will not cause symptoms or shorten an individual's life. Such overdiagnosis leads to overtreatment when these “pseudo-diseases” are conventionally managed and treated as if they were real abnormalities; because these findings have a benign prognosis, treatment can only do harm. More broadly defined, overdiagnosis happens when a diagnostic label is applied to people with mild symptoms or at very low risk of future illness, for whom the label and subsequent treatment may do more harm than good.[3]

Among the drivers of overdiagnosis are technological developments producing ever more sensitive imaging and biomarker tests, and changing disease and treatment thresholds that medicalize more people.[4] For example, detection of indolent breast lesions is now recognised as an established risk of mammography screening [5]; widened definitions of chronic kidney disease label many asymptomatic seniors as diseased [6]; lowered thresholds increase concerns about overdiagnosis of attention deficit hyperactivity disorder [7]; and more sensitive imaging methods are causing the treatment of large numbers of potentially benign pulmonary emboli.[8]

It's important to note there is a complex interrelationship between overdiagnosis and overtreatment—which can occur for many reasons other than overdiagnosis. If we consider the narrow definition of overdiagnosis—where someone is diagnosed with a “disease” that will not progress or harm them—overdiagnosis generally leads to overtreatment. Writing about overdiagnosis in 1998, Black described the cycle of increasingly sensitive tests causing more “pseudo-disease” to be diagnosed and conventionally treated.[9] Because prognosis of “pseudo-disease” is generally benign, there is a perception that patients do well on treatment, reinforcing belief in the value of treatment to the widened patient pool, and in turn fuelling further overtreatment.[9] In other situations, inappropriate overtreatment can



occur where there is a legitimate clinical diagnosis, and in some circumstances a degree of overtreatment may be warranted, for instance, the early use of parenteral antibiotics in someone suspected of having bacterial meningitis.

Considering the broader definition of overdiagnosis—involving the medicalisation of people with mild problems or at very low risk of disease—it becomes more difficult to define what constitutes subsequent overtreatment. Those judgements will depend on a complex mix of evidence about individual risk, prognosis, and treatment benefit–harm calculations, combined with the personal values and preferences inherent in any decision-making. Cognisant of this complex context, this essay explores how the production, analysis, and interpretation of evidence—whether from individual studies or systematic reviews—might be improved to better inform those judgements, and to better understand and combat the challenges of overdiagnosis and related overtreatment.

### **Average Therapeutic Trial Results Can Mislead**

It's widely recognised that average treatment effects estimated by systematic reviews of primary therapeutic trials don't really apply to any single patient, and an average benefit can mask both positive and negative effects in different patient subgroups. This leads to treatment of patients who don't benefit, and may suffer harms. Almost two decades ago, advocates of the then emerging evidence-based approach stressed the importance of a nuanced application of evidence from primary trials and systematic reviews for individuals, taking into account a person's absolute risk of an outcome and the need to weigh up potential benefits and harms.[10]

More recently Kent and colleagues cited examples where positive clinical trial results masked a lack of meaningful benefit for those at lower risks of illness, including trials involving statins, anticoagulant therapies, and some common surgical procedures.[11] The authors argued that this problem of trials masking the “heterogeneity of treatment effects” can result in guidelines that promote overtreatment, as well as undertreatment, and they recommended estimation of treatment effects after stratifying trial participants according to baseline risk.

Similarly, in a presentation to the inaugural Preventing Overdiagnosis Conference in 2013, Llewelyn re-analysed trial data involving medication for diabetic microalbuminuria and identified subsets of trial participants according to their specific disease stage, finding that many people were likely being treated without benefit.[12] The hope is that better stratification of people by disease stage, or baseline risk of relevant outcomes, will enable better identification of who will benefit and who will be harmed by an intervention, potentially informing the development of more appropriate diagnostic cut-points and treatment thresholds, ultimately reducing overdiagnosis and overtreatment.

### **We Need More Nuanced Evaluation of Tests, Too**

Just as with the average treatment effects of therapeutics, the average accuracy of a test does not apply to everyone.[13] Moreover, disease is often not simply “present” or “absent”, but rather exists on a continuous scale.[14] Hence, assessing a diagnostic test is more complex than simply knowing its average sensitivity and specificity or how well it detects the presence or absence of a disease.[13] There is a need to know how well diagnostic tests detect subsets of clinically meaningful, as opposed to non-meaningful, abnormalities or disease stages. In other words, it's important to diagnose or identify the spectrum of individuals for whom a disease label and associated intervention will do more good than harm.

A more sophisticated approach is particularly needed when assessing newer, highly sensitive tests—often more costly and burdensome to perform—that can identify earlier, milder, or indolent abnormalities or disease stages. For example, computed tomography pulmonary angiography has led to a dramatic increase in detection of small “sub-segmental” pulmonary emboli, of uncertain clinical significance, with emerging debate over whether many people are being treated unnecessarily with anticoagulants.[8] As a result, pulmonary embolism has been described as a “model for the modern phenomenon of overdiagnosis”.[1]

### **The Benefits and Harms of Expanding Disease Definitions**

A recent investigation of panels that change disease definitions found that while lowering diagnostic thresholds and widening definitions are common, few panels reported on the potential harms of expanding the numbers of people who qualify for a diagnosis.[4] Among

panels that had made recent changes to the definitions of common conditions—such as hypertension, attention deficit hyperactivity disorder, and myocardial infarction—the study also found widespread conflicts of interest. For panel publications that included disclosure sections, around 75% of panel members disclosed multiple financial ties to pharmaceutical companies active in the relevant therapeutic area.

Without doubt there are many cases where lower diagnostic thresholds and earlier diagnosis and treatment of disease or risk factors can improve health outcomes. For example, early diagnosis of hypertension helps precipitate preventive lifestyle changes or medication use. However, increasing medicalization may bring harms as well as benefits, as many others have highlighted in debates about “disease mongering”.[15] When, for example, conditions such as restless legs syndrome or female sexual dysfunction are constructed and promoted as being widespread and severe,[15] there are legitimate concerns that diagnosing and treating those with mild problems may do them more harm than good.

## **Improving the Evidence Base to Combat Overdiagnosis and Overtreatment**

As a matter of urgency, the potential for overdiagnosis and related overtreatment should be routinely considered for inclusion in the introduction and discussion sections of reports of studies of therapies, studies of diagnostic test accuracy, systematic reviews of those studies, clinical guidelines, and changes to disease definitions (Box 5). Second, there is a clear need for more research—both original studies and reviews of studies—into the nature and extent of overdiagnosis and related overtreatment within specific conditions—as, for example, has occurred with studies on the risks associated with mammography.[5] Third, the potential harms associated with new treatments and tests, or expanded disease definitions, demand much greater attention in primary studies and reviews.

### **Box 5. Summary of Suggestions for Improving the Evidence Base to Combat Overdiagnosis and Related Overtreatment**

1. Routine consideration of overdiagnosis and related overtreatment in the introduction and discussion sections of primary studies and systematic review articles about tests and treatments

2. More condition-specific studies and reviews on the risk of overdiagnosis and related overtreatment—e.g., diagnosis of pulmonary embolism
3. More rigorous routine evaluation of potential harms of treatments, tests, and changes to disease definitions
4. In studies and reviews of studies of therapies, clearer stratification by baseline risk, to better identify treatment thresholds where benefits are likely to outweigh harms
5. In studies and reviews of studies of test accuracy, more clarity about which target condition or spectrum of a disease is being considered, with a shift from a dichotomous “disease/no disease” frame to a “spectrum of disease severity” frame, and a linking of test accuracy to consequences for treatment and patient outcomes
6. Panels that review and change disease definitions that are free of conflicts, and routinely consider evidence for potential harms as well as potential benefits of the changes they propose

For evaluation of treatments, more clarity is required about the specific definitions of diseases being treated in primary treatment studies and subsequent systematic reviews. As per the recommendations of Kent and colleagues,[11] clearer stratification of groups at varying degrees of baseline risk or disease stage is needed, to better identify treatment thresholds at which the harms of treatment start to outweigh benefits. Sometimes this will require re-analysis of large (e.g., pooled individual participant) datasets, underscoring the need for access to raw data from trials.

For primary studies and reviews of studies of diagnostic test accuracy, there is a need to make explicit exactly which stages or spectrum of a target disease is being considered—also referred to as the “target condition”.[14] Where possible, it may be desirable to shift the paradigm from a dichotomous frame—disease presence versus absence—to thinking about a spectrum of disease severity. Moreover, when diagnostic studies show improved detection (or exclusion) of specific disease stages, researchers should try to link the consequences of such improved diagnostic accuracy to subsequent treatment decisions. Ideally, the consequences of such changed treatment decisions for patient outcomes might also be addressed.[16] Such elaborations to conventional diagnostic test accuracy studies would

help identify at what diagnostic disease spectrum thresholds subsequent treatments will do more good than harm.

And, finally, the need to improve the process of disease definition—with awareness of the dangers of overdiagnosis and overtreatment—is being increasingly accepted, with international organisations, including the Guidelines International Network, currently looking to develop new guidance. While a detailed debate will ensue in coming years, we believe several key principles might underpin the reform of how disease definitions are changed: panel members should be free of financial and reputational conflicts of interest; strong evidence, ideally from randomised trial data, should demonstrate that the use of new criteria will meaningfully reduce mortality and/or morbidity; and potential benefits and potential harms of labelling and treatment using the new criteria should be explicitly investigated and reported.

## Conclusions

We offer these suggestions as part of the wider scientific debate underway on how to safely and fairly wind back the harms of too much medicine.[17] We are hopeful that a heightened attention to the dangers of overdiagnosis and related overtreatment may lead to an enhanced evidence base on these topics. This, in turn, will help produce fairer, more rational, and less wasteful health care systems, built on a reformed process of disease definition that offers diagnostic labels and medical interventions only to those likely to benefit from them.

## Acknowledgments

The genesis of this article was a special session on overdiagnosis at the 21st Cochrane Colloquium, held in 2013 in Quebec City, Canada.

## Author Contributions

Wrote the first draft of the manuscript: RM. Contributed to the writing of the manuscript: RM DH KM. [ICMJE](#) criteria for authorship read and met: RM DH KM. Agree with manuscript results and conclusions: RM DH KM.

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## **Chapter 8**

## **Discussion**

Ray Moynihan



## Summary

This final chapter offers a summary of the thesis findings, explores their limitations and strengths within the context of the wider literature, outlines implications and makes some suggestions for future research and policy responses to help prevent overdiagnosis or ameliorate its impacts.

## Summary of findings

The initial scoping of the overdiagnosis literature found considerable research evidence of varying quality about the problem of overdiagnosis, across many conditions.[1] The evidence was most extensive and developed in relation to the risk of overdiagnosis associated with cancer and cancer screening, including for example breast,[2] prostate,[3] and thyroid cancers.[4] The overview, which arose from the scoping and appears as chapter 2, also described differing but related pathways that can lead a person to be overdiagnosed, including via screening, via expanded disease definitions and via the detection of “incidentalomas”. In addition the overview explored a range of inter-related causes of the problem: technological change, commercial forces and cultural enthusiasm for early detection.

The cross-sectional study of the expert guideline panels operating across 14 common conditions featured in chapter 3, found that over the past decade when panels reviewed disease definitions, they often proposed changes which would increase the proportions of the population diagnosed, by creating pre-diseases, by lowering diagnostic thresholds or by changing diagnostic assessment processes to enable earlier or increased detection of disease.[5] Among the 16 publications from expert panels analysed, coverage of the potential harms of proposals to change definitions was generally brief and cursory, and none reported on any investigation of the potential for overdiagnosis arising from panel proposals.

The study reported in chapter 3 also found widespread and direct financial conflicts of interest among these highly influential panels which set the boundaries defining human diseases and medical conditions. These findings are in direct contrast to repeated recommendations from the Institute of Medicine,[6,7], IOM, to wherever possible, constitute guideline panels without members with financial ties, in part to restore public trust in guidelines. For the 14 publications which included disclosure sections, 75% of panel members disclosed multiple financial ties to a median of seven pharmaceutical or device manufacturers. Ties included working as speakers, consultants, advisers or researchers. In addition 12 of 14 panels were chaired by people disclosing multiple financial ties.

The study also found that companies to which guideline panel members were most commonly tied were all selling or developing medications for the specific conditions and

diseases on which those same panel members were deliberating. For example companies marketing hypertension drugs—Bristol-Myers Squibb, Merck, Novartis—each had financial ties to eight of the eleven members of the panel that created the new diagnostic category pre-hypertension. In another example 57% of the panel that described “pre-dementia” disclosed ties to a median of five companies each. Eli Lilly - a company developing a drug in the area - had financial ties to almost one third of panel members. In order to assess how the quantum of conflicts was affected by repeated recommendations in IOM reports, we assessed disease-defining panels which published before and after 2012. Post 2012 we found a decrease in the median number of companies to which members had ties, from seven to four, but no difference in the high proportion of panel members reporting conflicts.

The 2013 examination of the definition of chronic kidney disease, CKD, reported in chapter 4, found an intense and on-going controversy within the scientific literature, dating back to the inception of the framework which launched the new disease definition in 2002.[8] A key criticism of the CKD definition, and a concern repeatedly expressed in the literature, is that it does not take into account age as a factor when assessing and categorizing kidney function, and as a result the very broad definition of CKD unnecessarily medicalises and overdiagnoses many older people. Yet in the face of on-going criticism and concern, the organisations and experts which launched the new disease framework have consistently defended their decisions and diagnostic thresholds, with only minor modification, arguing that thresholds for diagnosis are based on meaningful increases in the risks of future adverse events. Emblematic of a much wider problem, risks are portrayed as diseases: in this case a risk for heart disease is effectively described as “chronic kidney disease.” As reported in chapter 4, an important proportion of the experts who created and have consistently defended the controversial definition have disclosed financial ties to pharmaceutical or device manufacturers, and the organisations which have auspiced and promoted the new definition have relied heavily on funding from a consortia of pharmaceutical companies.

The 2014 national community survey reported in chapter 5 had a number of key findings.[9] Only a small minority, 10%, (95% CI 8%-13%) of respondents reported that they had been informed about the risk of overdiagnosis by a doctor. For those who reported being screened, only 18%, (95% CI 11%-28%) of those screened for prostate cancer, and 10% (95% CI 6%-

15%), for breast cancer, reported being informed of the risk of overdiagnosis, despite that risk being well established in the medical literature. A large majority, 93%, (95% CI 90%-95%) agreed that along with screening benefits, people should be informed about the risk of overdiagnosis. The number of people likely to take a hypothetical genetic screening test, 49% (95% CI 44%-53%) waned significantly to 28%, (95% CI 25%-33%) when participants were told disease predictions could be uncertain and inaccurate. In relation to public opinions about expert panels which define disease, a majority, 78%, (95% CI 74%-82%) felt it inappropriate that panel members have financial ties to pharmaceutical companies, echoing recommendations from IOM reports.[6,7]

The qualitative analysis of responses to the open-ended survey question - "what do you think the term overdiagnosis means?" - is reported in chapter 6.[10] Following independent analysis by two investigators of the themes emerging from responses, the study found 40% thought overdiagnosis meant exaggerating a condition, diagnosing something that was not there, or too much diagnosis. 24% of respondents thought overdiagnosis meant overprescribing, overtesting or overtreating. No respondent associated overdiagnosis with screening.

### **Limitations and strengths in context of wider literature**

There are important limitations attached to each of these research projects, as identified explicitly in the preceding chapters. The overview published as a result of the initial scoping of the literature on overdiagnosis was not a systematic review: the literature covered many conditions, many different study designs and was extremely heterogeneous. In chapter 3, the study of expert disease panels had no "control" group of panels which made no changes to definitions, so no claims are made about causal factors determining decisions to expand definitions. In particular no findings are made that there is a causal link between panel member financial ties and decisions to widen disease definitions. An additional limitation was that the study did not investigate the nature or proportion of non-financial ties, also known as intellectual or reputational conflicts, and the influence these may have on the guideline decisions regarding disease definitions.

For the case study involving examination of the controversy over chronic kidney disease, there are no randomised controlled trial data which enables estimates of the extent of overdiagnosis, as is the case with some cancer screening programmes. Unlike the situation for cancer screening, for many of the non-cancer conditions where there is concern that definitions have been inappropriately widened, current evidence would suggest the existence of a *risk* of overdiagnosis, rather than being able to reliably estimate and quantify the *magnitude* of that risk.

For the national community survey of Australians, as outlined in chapter 5, an important limitation arises from the modest response rates, though concern about the possibility of systematically different responses from those unable to be contacted is mitigated to some extent by the general representativeness of the survey's random sample. The use of 7-item Likert scales can also present difficulties in relation to a participant's ability to discriminate between two items – for example “mostly likely- somewhat likely” – though, as Table 8 shows, all similar responses were combined in our main analysis. (e.g. all “likely” were combined and all “unlikely” were combined) An important limitation of the qualitative analysis of responses to the open-ended questions is that survey participants only had limited time to think through their answer before responding.

Along with limitations, there are a number of important strengths of the thesis research projects. The results of the initial scoping offered a concise and accessible summary of the evidence and overview of the problem of overdiagnosis. The resulting article has since been well-cited, attracted much public attention via media coverage,[11] and helped raised the profile of the problem globally. The article also helped launch two important global projects which have run in parallel with the thesis, the *Preventing Overdiagnosis* international scientific conferences,[12] and the series in *The BMJ* on expanding disease definitions.[13] Both projects arose in part from the initial scoping of the literature for this thesis, which identified a need for an annual international scientific meeting where the emerging science of overdiagnosis could be shared, and a need to focus more research attention on the problem of expanding disease definitions and the subsequent risks of overdiagnosis. Informed by many different research studies, the initial scoping and overview is strongly indebted to the 2011 book, *Overdiagnosed: making people sick in the pursuit of health*, [14] written

by clinician-researchers based at Dartmouth college in the United States, who have all contributed much to the evidence-base, and helped raise public and professional awareness of the problem.

Key strengths of the expert panel cross-sectional study were novelty and timeliness: this was the first study to systematically investigate panels which review and change common disease definitions in order to analyse their decisions and their financial conflicts of interest. Previously Schwartz and Woloshin had looked at proposed changes to four selected conditions, and analysed implications for disease prevalence,[15] and many other authors have investigated the conflicts of interest of guideline panels.[16,17] None however have investigated the specific subset of panels whose deliberations have implications for disease definition or diagnostic thresholds. To my knowledge, our study was the first to bring these differing strands of inquiry together in a systematic way, in order to bring more scientific scrutiny to this lesser-investigated pathway to overdiagnosis: expanding disease definitions. Notwithstanding important limitations, the findings of widespread financial ties involving the vast majority of panel members, including chairs, in direct contrast to IOM recommendations for more independence, raise questions about the legitimacy of panel proposals which widen definitions and directly benefit companies to which panel members are tied. The results reinforce calls for reform of the way guideline panels are constituted,[18] and disease definitions are changed.

While the cross-sectional study of expert guideline panels provided a snapshot at a certain point in time across many conditions, the strength of the examination of the chronic kidney disease case study was that it looked back over the past decade of debate about overdiagnosis within the literature around a single condition. Where the cross-sectional study found extensive financial ties at a given point of time, the case study found that over time organisations funded by industry and experts with financial ties to industry, repeatedly worked to defend controversial decisions against sustained scientific criticism and concern about overdiagnosis. Again, the findings do not establish a causal link between industry ties and particular positions, but the appearance of major conflicts of interest, in direct contrast to professional recommendations, are evident.

In the context of growing calls for better communication about the problem of overdiagnosis,[19] and greater public awareness of the harms as well as benefits of screening,[20] the national survey was the first time the general community has been asked explicitly about overdiagnosis, how well they were informed, and what their views were on providing such information. In line with a small internet-based study in the United States by Wegwarth and Gigerenzer, which focussing more narrowly only on those invited for screening,[21] our community telephone survey of landline and mobile-only users found few survey participants reported being informed about overdiagnosis, including those who reported being screened for prostate or breast cancer. Another survey from Waller and colleagues in the United Kingdom,[22] found that the overdiagnosis information being provided to women about breast cancer screening was not well understood and was not enough for informed consent, underscoring the challenge of communicating complex and often counter-intuitive information.

Against a backdrop of growing use of molecular diagnostics and direct-to-consumer marketing of genetic testing, our general community survey found public enthusiasm for genetic screening may well be modified significantly by information about uncertainties and potential harms associated with such tests. And for the first time the survey sought views on the financial ties of panels which set disease definitions - finding considerable agreement between participant opinion and recommendations of the IOM.[6,7] The strength of the qualitative analysis of community understanding of the term overdiagnosis, is that it helps bring the community voice into the debate about the problem, although that wider conversation is only just beginning.

### **Caveats and cautions**

Before moving to discuss the way evidence is already informing action, and the implications of the thesis findings, a few important caveats and cautions are warranted. Given that research in overdiagnosis is axiomatically about investigating the potential harms of medical interventions, in attempting to reduce these harms it would seem critically important to be cognisant of trying to minimise any unintended adverse consequences. In recognition of this, it follows that the evidence establishing the problem of overdiagnosis is not overstated, and that its limitations are clearly articulated.

Even with cancer screening, where the science is most well-advanced and numerical estimates of the extent of overdiagnosis appear regularly in the literature, sometimes derived from randomised trials or systematic reviews, there are vigorous debates about methodology, and wide variations in numerical estimates. For non-cancer conditions, while numerical estimates do appear, as featured in the overview on chapter 2, the evidence-base is not as well developed.

Importantly, strong arguments appear in the overdiagnosis literature that some degree of overdiagnosis is inevitable, particularly in screening programmes, [23] and that winding back the risk of overdiagnosis may come at the risk of increasing underdiagnosis. Any strategies to combat overdiagnosis must be cognisant of this risk, focussing on identifying that proportion of overdiagnosis that is avoidable and preventable. A related caution arises because much of the evidence for overdiagnosis comes from population-based analysis, rather than the direct experience of harm to individual people. For example, while there is now convincing evidence overdiagnosis is a risk of breast cancer screening, and many women will be diagnosed with cancers that would never have harmed them, it is almost impossible to identify an individual woman who has been overdiagnosed. However, while it is important to acknowledge the fact that some degree of overdiagnosis is inevitable, and that it is hard to identify overdiagnosed individuals, this is not a justification for nihilism in the face of the problem and should not deter the development of a range of potential mitigation strategies.

### **Evidence-informing action**

There is a variety of research already underway internationally describing the problem, exploring its causes, and developing potential responses, both generally and condition-specific, as evidenced by both a small but burgeoning literature and the many contributions to the *Preventing Overdiagnosis* conferences at Dartmouth in 2013, Oxford University in 2014, and the forthcoming event to be held at the National Cancer Institute in Washington DC in September 2015.[12]

In the move from research to response, there are now several examples where the science on overdiagnosis is motivating evidence-based evaluation of mitigation strategies. For example,



as a result of evidence suggesting potentially widespread overdiagnosis of pulmonary embolism,[24] an observational study is now underway to evaluate whether it is possible to reduce unnecessary diagnosis and treatment of some small and potentially benign clots.[25] In the field of cancer, leading researcher-clinicians are responding to the problem of overdiagnosis by suggesting a suite of possible solutions,[26] including more communication about the problem, changes to terminology that removes the word cancer from early abnormalities with a generally benign natural history, and where appropriate, the evaluation of observational registries, and watch and wait strategies. In some cases, evidence about potential or actual harm from overdiagnosis has contributed to official recommendations against screening programmes, for example, for chronic kidney disease[27] and prostate cancer.[28] In some places health systems and health sectors are prioritising overdiagnosis, as in Quebec, Canada, where the professional medical association has brought many stakeholders together to try to develop a province-wide action plan to combat it.[29] Communicating about overdiagnosis is also receiving more research attention, with randomised trials evaluating the best ways to present information to people,[30] and surveys investigating how well the emerging information provision is informing people.[22]

## **Implications and recommendations arising from the thesis**

While there is existing evidence of varying quality across many conditions, and more research projects underway, the potential size and significance of the problem suggests a clear need for more research into the nature of overdiagnosis, its causes, consequences, and solutions. As discussed below in more detail, four key implications and recommendations arise from the findings of this thesis:

- Synthesis and aggregation of overdiagnosis evidence into an accessible repository
- More investigation of expanding disease definitions and their impacts on overdiagnosis
- Reform of the process of disease definition
- New international research collaborations to understand and combat overdiagnosis

### **Synthesis and aggregation of evidence into overdiagnosis repository**

With the growing research evidence and interest in overdiagnosis, there is an urgent need for an accessible synthesis and aggregation of the evidence, condition by condition, available for the public, professionals and policy makers. Such an overdiagnosis repository could contain: information about research methods; estimates of the magnitude of the risk of overdiagnosis for each condition where evidence exists; estimates of costs and opportunity costs; estimates of the burden of overdiagnosis-related harms; key limitations around the evidence; and strategies for mitigating risk of unnecessary diagnoses, ranging from adjusting policy levers that can discourage unnecessary diagnoses, to creating aids for shared decision making in the clinical setting.

Currently information and evidence about overdiagnosis is available in a highly fragmented way, chiefly in articles published across a wide spectrum of journals and conditions. Similarly the experiences of organisations around the world which are adopting policy or practice changes designed to address overdiagnosis are not easily available to others seeking to learn from them. Undertaking the suggested aggregation and synthesis of current evidence would also reveal important gaps in the existing literature and point to future research projects. In addition, it could lead to the development of “tool kits” for health managers, and clearly articulated policy processes for policy-makers interested in preventing overdiagnosis.

### **More investigation of expanding disease definitions and impacts on overdiagnosis**

The most important implication for research arising from this thesis is that, alongside the growing investigation of the risk of overdiagnosis associated with cancer screening, more research attention is required to investigate the risk of overdiagnosis caused by the way disease definitions and diagnostic procedures are widening the proportions of populations labelled as diseased. We need to know much more about how and why the definitions of common conditions are changing, and how and why expert panels are proposing changes to those definitions. While the study of multiple conditions will allow identification of general patterns, specific investigations of how and why particular disease definitions have changed over time will also enable more informed and constructive responses to the problem of inappropriately widened conditions, including “pre-diseases” which label increasing proportions of the healthy populations.. Most significantly, research is required to investigate the implications of these expanding definitions for labelling people as suffering

from “diseases” or “conditions” that will never cause them harm, for whom a diagnosis and subsequent treatment will axiomatically do more harm than good.

Research in this field needs to precisely examine the way threshold changes impact on the benefit-harm ratios for those labelled and subsequently treated, and to investigate examples of conditions where raising thresholds[31] may be appropriate. The series currently appearing in *The BMJ* on expanding disease definitions and the risk of overdiagnosis - which has covered a range of common conditions including pulmonary embolism,[24] attention deficit hyperactivity disorder,[32] and gestational diabetes[33] - is contributing to a greater awareness of the problem, but more research is required on optimum methods for measuring non-cancer overdiagnosis, and the precise nature and extent of the problem across specific conditions, in order to inform effective responses in terms of practice and policy change.

**Reform the process of disease definition: independent, representative, evidence-based**

As to potential policy solutions, a key implication arising from this thesis is the need for major reform of the process of disease definition. It is inappropriate and indefensible that expert panels dominated by those with multiple direct financial relationships with interested companies are lowering thresholds and labelling growing populations of “patients” among the previously healthy. Similarly it is inappropriate that there is currently no routine investigation of the risk of overdiagnosis and related overtreatment when disease definitions are being reviewed and changed. Notwithstanding the limitations associated with the thesis findings, reform of both panel constitution and their processes are indicated. In line with IOM recommendations, derived from solid independent assessment of the large body of evidence about conflicts of interest, and echoed in findings arising from the thesis research, panels which define human disease will likely serve the public interest far better if they were more independent from vested interests, more broadly representative, and are informed by the best evidence about the potential harms as well as the potential benefits of their decisions, as outlined in the essay published with colleagues in *PLOS Medicine*, which appears as chapter 7 of this thesis.[34]

To inform policy reform, research projects which investigate new ways to review disease definitions or diagnostic thresholds could focus on specific conditions where controversy

around expanded definitions is high, and potential for overdiagnosis is significant, including for example chronic kidney disease, gestational diabetes, or pre-dementia. Templates for more independent evidence-informed and broadly representative expert panels already exist, notably the current series of Pathways to Prevention conferences hosted by the National Institutes of Health,[35], NIH, and the former series of NIH consensus conferences,[36] which explicitly used a three-step process: a panel was assembled with professional and public representatives who were free of reputational and financial conflicts of interest; the panel was informed by systematic literature reviews; and testimony was sought from (potentially conflicted) researchers and clinicians active in the area.

### **New multi-national research collaborations on overdiagnosis**

In order to undertake the proposed research agenda and inform policy reforms outlined above, new international research alliances or collaborations will be required, affording the chance to strategically and systematically address the multi-faceted problem of overdiagnosis. Such collaborations would ideally involve consumer/citizen organisations, have a patient-centred and shared-decision making focus, and as far as possible be independent from professional and commercial groups with interests in maximising the size of patient populations.

A number of collaborative efforts arising from the *Preventing Overdiagnosis* scientific conferences are already underway to refine overdiagnosis definitions, research methods and optimum communication strategies. More innovative international alliances and collaborations of researchers, clinicians and consumers may well emerge from the conferences. Others are also advocating similar multinational collaborations to better understand and address overdiagnosis.[37] Such collaborative efforts could draw on, or work with existing international collaborative efforts including the Cochrane Collaboration and its review groups, and the many centres and networks specialising in evidence-based approaches globally. In order to understand and address the many causes and consequences of overdiagnosis in healthcare, greater cooperation and collaboration will be essential.

## **Conclusions**

The increasing recognition of the need to address overdiagnosis[19] is part of a wider awareness of the need to try and wind back the harms of too much medicine, in order that healthcare resources might be spent where they are most needed. Many initiatives have been launched in recent years to tackle the problem of excess, by a range of leading medical journals, professional and consumer groups and not-for-profit foundations, including Less is More,[38] Choosing Wisely,[39] Too Much Medicine,[13] the Right Care Alliance,[40] and Preventing Overdiagnosis.[12] In Europe, as Brodersen and colleagues describe, the emerging movement within primary care for “quaternary prevention” is similarly focussing on helping steer people away from medicalisation, diagnosis, testing and treatment likely to cause them more harm than good.[41] The movement is gaining increasing support as a way to combat the dangers of iatrogenic harm,[42] and is related to other moves within general practice organisations to re-think guidelines in ways that prevent unnecessary diagnoses and overtreatment.[43] In addition, as climate change mitigation becomes a reality, moves to avoid waste and overuse in medicine will be increasingly be seen as one of the paths towards a more sustainable and less-polluting healthcare system, as identified in a report in late 2014 from the Academy of Royal Medical Colleges in the United Kingdom: “Reducing waste in the clinical domain has a triple imperative; it improves value, lowers costs and reduces CO2 emissions.”[44] While all these initiatives are related by a desire to prevent harm and waste, the differentiation of scientific research specifically on overdiagnosis will continue.

A key challenge in responding to medical excess is the wide range of powerful forces driving it, be they technological, commercial, professional, personal or cultural. Commonly with the best of intentions medicine has long promoted the benefits of early detection, and championed the value of diagnosing and treating disease, without a commensurate enthusiasm for the rigorous evaluation of potential harms. The science of evaluation continues to live in the shadows of the science of innovation. Yet as new molecular diagnostics and genetic testing move increasingly from the lab into the clinic, as advanced imaging enables the detection of ever-tinier abnormalities, and as the proliferating self-monitoring health technologies becomes embedded in the marketplace as symbols of consumer empowerment, a new wave of overdiagnosis and the over-medicalisation of marginal risk is virtually inevitable, potentially bringing much more harm and wasting

resources that could be far better spent preventing and treating genuine illness. A necessary, though not sufficient, condition for meeting that challenge, will be an enhanced evidence-based assessment of the risks of overdiagnosis, and the aggregation, synthesis and dissemination of that evidence to inform personal, public, professional and policy responses.

The scientific debate about overdiagnosis is a debate grounded in evidence. As the evidence-based approach has grown in strength over recent decades, the many tools of its critical scrutiny have been aimed not just at treatments, but at diagnostic tests, including screening tests that target the healthy, where the risk of overdiagnosis is axiomatically greatest. What started with speculation has in many cases moved through evaluation and ultimately grown into convincing evidence of a public health problem, notwithstanding important debates around methods and uncertainties around estimates. Understandably, evidence suggesting iconic, popular and well-funded public screening programmes may be causing much unnecessary diagnosis and treatment, has not always been quickly or warmly welcomed.

As flagged in the introduction, ironically, the success of evidence-based scrutiny has helped precipitate something of a crisis in the evidence-based approach.[45] Increasingly rigorous and unbiased evaluation and analysis have helped expose how benefits of tests and treatments are generally overplayed and harms, including overdiagnosis, generally played down in much evidence, and how vested interests can distort and corrupt evidence, in everything from marketing to guidelines. Paradoxically the evidence “brand” has been debased as evidence has been hijacked, and proponents of evidence-based medicine are now calling for a rebirth of the approach.[45]

Writing in *The BMJ* in 2014 the Evidence-Based Medicine Renaissance Group flagged a number of proposed actions highly relevant to the findings and implications arising from this thesis. Among recommendations from the group were specific calls for policy-makers to resist “evidence” generated by vested interests, for independent funders to play a much bigger role in producing, synthesising and disseminating evidence, and for the medical research agenda to generate evidence on “how to prevent harm from overdiagnosis.”[45] Developing new ways to define human disease, much freer of vested interests, more independently funded and more cognisant of the risk of overdiagnosis, will surely be a key

feature of any such renaissance, reducing iatrogenic harm and helping redirect health resources to where they are genuinely needed.

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## About the Author

**Ray Moynihan** is an academic researcher, writer and author, with a background as a respected journalist, based in Australia with a global reputation.

Having reported across print, radio, television and social media, Ray's award-winning investigative medical journalism has attracted critical praise internationally. His 2005 book *Selling Sickness* was described in the *New York Times* as a "compelling case" and has been translated into a dozen languages. His fourth book, *Sex, Lies & Pharmaceuticals* was released globally in late 2010.

Since winning a Harkness Fellowship in healthcare policy in 1999, based at Harvard University, in addition to his journalism, Ray has developed an impressive body of academic research and writing resulting in articles in *The Lancet*, the *New England Journal of Medicine*, the *Medical Journal of Australia*, *PLoS Medicine*, and *The BMJ*, where he has been contributing columns since 2011.

Between 2006 and 2012 Ray was a conjoint lecturer at the University of Newcastle, in Australia, and since 2012 he has been a Senior Research Fellow and PhD candidate, based at the Centre for Research in Evidence-Based Practice, at Bond University in Australia.

Internationally recognized for his research on the business of medicine and more recently his work on the problem of overdiagnosis, Ray is often interviewed by media globally and regularly invited to give presentations at universities, conferences and workshops around the world.

With colleagues in Australia and globally, Ray has initiated and helped organised the highly successful series of international scientific conferences called *Preventing Overdiagnosis*, the next scheduled to take place at the National Cancer Institute in the United States in September 2015.



## **Appendix 1.**

# **Bond University**

## **“Medical Overdiagnosis”**

16 January, 2014

Questionnaire version 8 (including pilot changes)

**[PROGRAMMER NOTE:**

- Use standard SMS list
- Use standard RR1 list]

**\*INTRODUCTION & SCREENING**

\*(PHONE ANSWERER)

INTRO1: Good (morning/afternoon/evening) my name is (...) and I am calling from the Social Research Centre on behalf of Bond and Sydney Universities.

We're doing a short survey across Australia about community views on the way doctors diagnose diseases. This is an emerging issue and the results will help researchers find better ways for doctors to communicate about the risks and benefits of medical tests and treatments.

1. Continue

\*(LANDLINE)

INTRO2a: We would like to speak to the person in your household who is aged 18 years or over and who had the LAST birthday? Would that be you?

[REINTRODUCE IF NECESSARY: Good (morning/afternoon/evening) my name is (...) and I am calling from the Social Research Centre on behalf of Bond and Sydney Universities. We're doing a short survey across Australia about community views on the way doctors diagnose diseases. This is an emerging issue and the results will help researchers find better ways for doctors to communicate about the risks and benefits of medical tests and treatments.]

1. Yes (continue)
2. Not a good time: appointment (MAKE APPOINTMENT)
3. Household refusal (GO TO RR1)
4. Language difficulty (NO follow up) (GO TO TERM2)
5. Wants more information before participating (GO TO INFO1)
6. No one aged 18+ in household (GO TO TERM1)
7. Queried about how telephone number was obtained (GO TO TEL\_LAND)

\*(MOBILE)

INTRO2b. Can I ask whether you are aged 18 years or over?

1. Yes (continue)
2. Not a good time: appointment (GO TO MOB1)
3. Mobile answerer refusal (GO TO RR1)
4. Language difficulty (NO follow up) (GO TO TERM2)
5. Wants more information before participating (GO TO INFO1)
6. Under 18 years of age (GO TO TERM1)
7. Queried about how telephone number was obtained (GO TO TEL\_MOB)
8. Queried why mobile was called (GO TO TINFO\_MOB)

\*(IF INTRO2a=5 OR INTRO2b=5 – MORE INFO REQUIRED)

INFO1. You can find more information online from the Social Research Centre website ([www.srcentre.com.au](http://www.srcentre.com.au), on the 'participants' tab under 'current surveys'. This includes links to the Bond University and the University of Sydney websites.)

1. Make appointment [PROGRAMMER NOTE: IF MOBILE GO TO MOB1, ELSE MAKE APPOINTMENT]
2. (Wants info but NO INTERNET) (COLLECT MAILING DETAILS THEN IF MOBILE GO TO MOB1, ELSE MAKE APPOINTMENT; SET UP GETDET!]

\*(QUERIED HOW LANDLINE NUMBER WAS OBTAINED)

TEL\_LAND Your telephone number has been chosen at random from all possible telephone numbers. We find that this is the best way to obtain a representative sample of people across Australia.

1. Snap back to previous question

\*(QUERIED HOW MOBILE NUMBER WAS OBTAINED)

TEL\_MOB Your mobile number was randomly generated by a computer. We're calling mobile phones as well as landlines so we can get a representative sample of people across Australia.

1. Snap back to previous question

\*(QUERIED WHY MOBILE WAS CALLED)

TINFO\_MOB One of the issues currently facing telephone survey researchers in Australia is the increasing proportion of households without a landline telephone. We are calling mobile phones as well as landlines so we can get a representative sample of people across Australia.

1. Snap back to previous question

\*(MOBILE SAMPLE)

MOB2. May I just check whether or not it is safe for you to take this call at the moment? If not, I am happy to call you back when it is more convenient for you.

1. Safe to take call
2. Not safe to take call
3. Respondent refusal (GO TO RR1)

\*(MOBILE SAMPLE)

MOB1. Just so I know your time zone, can you tell me which state you're in?

1. NSW
2. VIC
3. QLD
4. SA
5. WA
6. TAS
7. NT
8. ACT
9. (Refused)

\*PROGRAMMER NOTE – WRITE STATE / TERRITORY TO SAMPLE RECORD

[PREMOBAPPT IF INTRO2b=2 OR 5, OR MOB2=2 CONTINUE (mob appointment), ELSE GO TO INTRO3a]

\*(MOBILE SAMPLE NEEDING APPOINTMENT)

MOB\_APPT Do you want me to call you back on this number or would you prefer I call back on another phone?

1. This number (TYPE STOP, MAKE APPOINTMENT)
2. Another number (TYPE STOP, MAKE APPOINTMENT, RECORD ALT NUMBER)
3. Respondent refusal (GO TO RR1)

\*(ALL)

INTRO3a: Thank you. Now, I'm just going to run some details past you about the study....

1. Continue
2. Not a good time (MAKE APPOINTMENT)
3. Respondent refusal (GO TO RR1)
4. Language difficulty (NO follow up) (GO TO TERM2)
5. More info "go to [www.srcentre.com.au](http://www.srcentre.com.au), on the 'participants' tab under 'current surveys'. This includes links to the Bond University and the University of Sydney websites." (MAKE APPOINTMENT)
6. (Wants info but NO INTERNET: collect details to mail info sheet) (MAKE APPOINTMENT)



\*(ALL)

INTRO3b:

The survey has been approved by the Bond University Ethics Committees and participation is completely voluntary. You can choose not to answer any question or to cease the survey at any time. Your phone number was selected randomly, your answers will remain completely anonymous and we will not be recording this phone call. It will only take around 15 minutes to complete.

Would you like more information or would you be willing to participate in this important study?

[INTERVIEWER NOTE: If more information requested, read the abridged Participant Information Sheet. If potential participant doesn't want to be read information, offer to provide website details and arrange an appointment.]

1. Continue
2. Not a good time (MAKE APPOINTMENT)
3. Respondent refusal (GO TO RR1)
4. More info "go to [www.srcentre.com.au](http://www.srcentre.com.au), on the 'participants' tab under 'current surveys'. This includes links to the Bond University and the University of Sydney websites." (MAKE APPOINTMENT)
5. (NO INTERNET ACCESS: arrange to send information sheet) (MAKE APPOINTMENT)

\*(ALL)

MON: This call may be monitored for training and quality purposes but will NOT be recorded. Is that OK?

1. Monitor
2. Do not monitor

\*(ALL)

S1a. Thank you. Now, before we begin the survey, would you mind telling me your age?

1. (Record number in years) [RANGE 18 to 105]
2. (Refused) (GO TO S1b)

\*(IF S1a=2 – Refused age)

S1b. Could you please tell me which of the following age groups you are in?

1. 18-29
2. 30-49
3. 50-69
4. 70 and over
5. (Refused)

\*(ALL)

S2. As we are talking about the way doctors diagnose diseases and medical treatments which affect men and women differently would you mind confirming your gender?

[IF NECESSARY: we need to ask this question of everyone to make sure we ask people the right questions throughout the survey]

[INTERVIEWER NOTE: If 'refuse' or 'other', allocate at your discretion]

1. Male
2. Female

\*(ALL)

S3. What is the post code of the area in which you live?

1. (Record post code \_\_\_\_\_) [RANGE: 800 to 9999]
2. (Don't know)(Specify suburb)
3. (Refused)

[PROGRAMMER NOTE: DERIVE 'STATE' WHERE RESPONDENT CAN PROVIDE POSTCODE; IF  
NO ELIGIBLE POSTCODE PROVIDED ALLOCATE TO 'OTHER' STATE]

**\*SECTION A: GENERAL KNOWLEDGE ABOUT OVERDIAGNOSIS**

Just to start our survey...

\*(ALL)

A1. Have you seen or heard the term 'overdiagnosis' before today?

[IF NECESSARY: We are discussing overdiagnosis of medical illnesses, diseases and conditions].

1. Yes
2. No
3. (Don't know)
4. (Refused)

[PRE A2 IF A1=1 use A2i ELSE use A2ii]

\*(ALL)

A2i. What do you understand the term 'overdiagnosis' to mean?

A2ii. What do you think the term 'overdiagnosis' means?

[IF NECESSARY: We are discussing overdiagnosis of medical illnesses, diseases and conditions].

1. Response Given (Specify) \*(PROGRAMMER NOTE: Set up as full verbatim)
2. (Don't know / can't say)
3. (Refused)

\*(ALL)

A3. A generally accepted view is that overdiagnosis happens when people are diagnosed with a disease that would never have harmed them. This could be due to the condition being so slow developing or them displaying only very minor symptoms.

Given this explanation, have you seen or heard the term or concept of 'overdiagnosis'?

[IF NECESSARY: For example sometimes people are diagnosed with cancer, but that cancer would be so slow growing it would not cause them any harm in their lifetime, or a person with very mild problems may be diagnosed with a mental disorder such as ADHD.  
We are discussing overdiagnosis of medical illnesses, diseases and conditions].

1. Yes
2. No
3. (Don't know)
4. (Refused)

\*(ALL)

A4. Has a doctor ever told you that healthy people can be over-diagnosed as a result of being screened or tested for a disease?

1. Yes
2. No
3. (Don't know)
4. (Refused)

\*(ALL)

A5. Routine screening means testing healthy people to find signs of diseases such as cancer.

Do you think routine screening tests for healthy people are almost always a good idea?

1. Yes
2. No

3. (Don't know)
4. (Refused)

\*(ALL)

A6. Do you agree or disagree that routine screening tests for healthy people are important for their health?

PROBE: IS THAT COMPLETELY, MOSTLY OR SLIGHTLY AGREE / DISAGREE?

(RESPONSE FRAME) (DO NOT READ OUT)

1. Completely agree
2. Mostly agree
3. Slightly agree
4. (Neither agree nor disagree)
5. Slightly disagree
6. Mostly disagree
7. Completely disagree
8. (Don't know / Can't say)
9. (REFUSED)

\*(ALL)

A7. When healthy people are considering having a screening test - along with being told about the potential benefits of the screening test – do you agree or disagree that they should be informed about the potential risk of overdiagnosis?

[IF NECESSARY: For example a screening test for prostate or breast cancer, chronic kidney disease or other diseases and illnesses].

PROBE: IS THAT COMPLETELY, MOSTLY OR SLIGHTLY AGREE / DISAGREE?

(RESPONSE FRAME) (DO NOT READ OUT)

1. Completely agree
2. Mostly agree
3. Slightly agree
4. (Neither agree nor disagree)
5. Slightly disagree
6. Mostly disagree
7. Completely disagree
8. (Don't know / Can't say)
9. (REFUSED)

\*(ALL)

TS1\_Section A

**\*SECTION B: SCREENING EXPERIENCES**

\*(ALL)

B0. I will now ask you a few brief questions about your experiences with medical screening tests.

[PREB1a: IF S2=2 (female) GO TO PREB2; ELSE CONTINUE]

\*(S2=1 – Males only)

B1a Have you ever had a screening test, sometimes called a PSA test before for prostate cancer?

1. Yes
2. No (GO TO B3)
3. (Don't know) (GO TO B3)
4. (Refused) (GO TO B3)

\*(B1a=1 – had screening test)

B1b. Were you told about the risk of overdiagnosis (of this test)?

[IF NECESSARY: In other words, were you told by a doctor, GP, or the person who offered or administered the test that you may be diagnosed and treated for a cancer that would never have caused you any harm in your lifetime?]

1. Yes I was told
2. No I wasn't told
3. (Don't know)
4. (Refused)

[PREB2: IF S2=1 (male) GO TO B3; ELSE CONTINUE]

\*(S2=1 – Females only)

B2a Have you ever had a mammogram to screen for breast cancer?

[IF NECESSARY: "We are interested in finding out if women have had a screening test when they didn't have any problem in their breast, such as a lump, as opposed to having a 'diagnostic' mammogram, where there was a problem being investigated.]"

1. Yes
2. No (GO TO B3)
3. (Don't know) (GO TO B3)
4. (Refused) (GO TO B3)

\*(B2a=1 – had screening test)

B2b. Were you told about the risk of overdiagnosis (of this test)?

[IF NECESSARY: In other words, were you told by a doctor, GP, or the person who offered or administered the test that you may be diagnosed and treated for a cancer that would never have caused you any harm in your lifetime?]

1. Yes I was told
2. No I wasn't told
3. (Don't know)
4. (Refused)

\*(ALL)

B3. Have you ever had a genetic screening test?

[IF NECESSARY: A genetic screening test, or DNA testing, seeks to identify inherited diseases or diseases passed on through blood relations]

1. Yes
2. No
3. (Don't know)
4. (Refused)

\*(ALL)  
TS2\_Section B

**\*SECTION C: INTEREST IN GENETIC SCREENING**

\*(ALL)

- C1. Imagine that there was a genetic screening test which could analyse your genes and identify all the diseases you may ever get, for which some had effective treatments and some did not. Would you be likely or unlikely to have that screening test?

PROBE: IS THAT COMPLETELY, MOSTLY OR SOMEWHAT LIKELY / UNLIKELY?

(RESPONSE FRAME)

1. Completely likely
2. Mostly likely
3. Somewhat likely
4. (Neither likely nor unlikely)
5. Somewhat unlikely
6. Mostly unlikely
7. Completely unlikely
8. (Don't know)
9. (Refused)

\*(ALL)

- C2. Imagine now that the results of the genetic screening test were often uncertain, and the predictions could be wrong. Would you be likely or unlikely then to have that screening test?

PROBE: IS THAT COMPLETELY, MOSTLY OR SOMEWHAT LIKELY / UNLIKELY?

(RESPONSE FRAME)

1. Completely likely
2. Mostly likely
3. Somewhat likely
4. (Neither likely nor unlikely)
5. Somewhat unlikely
6. Mostly unlikely
7. Completely unlikely
8. (Don't know)
9. (Refused)

\*(ALL)

TS3\_Section C



**\*SECTION D: BREAST SCREENING (MALES VS FEMALES)**

\*(ALL)

D0. In this next section I'm going to describe a particular scenario about screening for cancer, then ask you some questions about that scenario. Sometimes people can find these questions personal or sensitive. If you are unsure how to answer or do not want to answer any question please let me know and I will move on.

[PROGRAMMER NOTE: create dummy variable to randomly assign males and females to relevant Option 1 and Option 2. Each respondent to respond to one scenario.]

\*(ALL) [PROGRAMMER NOTE: All respondents need to be assigned a code at RAND; minimum of 100 respondents per code]

RAND: "Random assignment of males and females to Option 1 and Option 2"

1. S2=2 + random assignment (Female, Option 1)
2. S2=2 + random assignment (Female, Option 2)
3. S2=1 + random assignment (Male, Option 3)
4. S2=1 + random assignment (Male, Option 4)

[PRED1: IF RAND=1, CONTINUE. ELSE GO TO PRED5]

\*(RAND=1 – Female, Option 1)

D1. Breast screening (mammograms) detects abnormal changes of cells in the breast as well as finding breast cancers. In some women these abnormal cells can progress to invasive cancer and in others they do not. It's estimated that if left untreated about one-third may progress to breast cancer over 10 years or more. That means that for about two-thirds of women these abnormal cells may not become cancer.

Imagine you had an abnormal breast screen and follow-up tests showed that there were abnormal cells found in your breast.

How concerned would you be about your result? Would you say...

[IF NECESSARY: 'Invasive' cancer means potentially life threatening.]

(RESPONSE FRAME) (READ OUT)

1. Extremely concerned
2. Moderately concerned
3. (Neither concerned nor unconcerned)
4. Not really concerned
5. Not concerned at all
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=1 – Female, Option 1)

D2. Abnormal breast cells are usually treated by surgery, radiation or drugs as in the case of breast cancer. Another approach is called watchful waiting, where doctors closely monitor the abnormal breast cells with regular mammograms and only treat if cells become more abnormal.

If research shows that watchful waiting is a safe and effective option, how do you think you would prefer to manage these abnormal cells? Would you say...

[IF NECESSARY: If people want more information on exactly what watchful waiting would entail - say, that's what research would determine.]

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)

5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=1 – Female, Option 1)

- D3. Thinking again about the previous scenario, if these abnormal cells in your breast were instead called pre-invasive breast cancer cells (rather than abnormal cells), would you be more concerned or less concerned about your screening test result?

(RESPONSE FRAME)

1. More concerned
2. (No difference)
3. Less concerned
4. (Don't know)
5. (Refused)
6. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=1 – Female, Option 1)

- D4. And if research shows that watchful waiting is a safe and effective option, how do you think you would prefer to manage these pre-invasive breast cancer cells? Would you say...

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)
5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

[PRED5: IF RAND=2, CONTINUE. ELSE GO TO PRED9]

\*(RAND=2 – Female, Option 2)

- D5. Breast screening (mammograms) detects pre-invasive breast cancer cells in the breast as well as finding breast cancers. In some women these pre-invasive breast cancer cells can progress to invasive cancer and in others they do not. It's estimated that if left untreated about one-third may progress to breast cancer over 10 years or more. That means that for about two-thirds of women these pre-invasive breast cancer cells may not become cancer.

Imagine you had a breast screen and follow-up tests showed that there were pre-invasive breast cancer cells found in your breast.

How concerned would you be about your result? Would you say...

[IF NECESSARY: 'Invasive' cancer means potentially life threatening.]

(RESPONSE FRAME) (READ OUT)

1. Extremely concerned
2. Moderately concerned
3. (Neither concerned nor unconcerned)
4. Not really concerned
5. Not concerned at all
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=2 – Female, Option 2)

- D6. Pre-invasive breast cancer cells are usually treated by surgery, radiation or drugs as in the case of breast cancer. Another approach is called watchful waiting, where doctors closely monitor the pre-invasive breast cancer cells with regular mammograms and only treat if cells become more invasive.

If research shows that watchful waiting is a safe and effective option, how do you think you would prefer to manage these pre-invasive breast cancer cells? Would you say...

[IF NECESSARY: If people want more information on exactly what watchful waiting would entail - say, that's what research would determine.]

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)
5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=2 – Female, Option 2)

- D7. Thinking again about the previous scenario, if these pre-invasive breast cancer cells were instead called abnormal cells (rather than pre-invasive cells), would you be more concerned or less concerned about your screening test result?

(RESPONSE FRAME)

1. More concerned
2. (No difference)
3. Less concerned
4. (Don't know)
5. (Refused)
6. (Respondent does not understand terminology / issues) (GO TO TS4)



\*(RAND=2 – Female, Option 2)

D8. And if research shows that watchful waiting is a safe and effective option, how do you think you would prefer to manage these abnormal cells? Would you say...

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)
5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

[PRED9: IF RAND=3, CONTINUE. ELSE GO TO PRED13]

\*(RAND=3 – Male, Option 3)

- D9. Breast screening (mammograms) detects abnormal changes of the cells in the breast as well as finding breast cancers. In some women these abnormal cells can progress to invasive cancer and in others they do not. It's estimated that if left untreated about one-third may progress to breast cancer over 10 years or more. That means that for about two-thirds of women these abnormal cells may not become cancer.

Imagine your wife, daughter, mother or close female friend had an abnormal breast screen and follow-up tests showed that there were abnormal cells found in her breast.

How concerned would you be about her result? Would you say...

[IF NECESSARY: 'Invasive' cancer means potentially life threatening.]

(RESPONSE FRAME) (READ OUT)

1. Extremely concerned
2. Moderately concerned
3. (Neither concerned nor unconcerned)
4. Not really concerned
5. Not concerned at all
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=3 – Male, Option 3)

- D10. Abnormal breast cells are usually treated by surgery, radiation or drugs as in the case of breast cancer. Another approach is called watchful waiting, where doctors closely monitor the abnormal breast cells with regular mammograms and only treat if cells become more abnormal.

If research shows that watchful waiting is a safe and effective option, how do you think you would prefer she manage these abnormal cells? Would you say...

[IF NECESSARY: If people want more information on exactly what watchful waiting would entail - say, that's what research would determine.]

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)
5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=3 – Male, Option 3)

- D11. Thinking again about the previous scenario and the same person, if these abnormal breast cells were now called pre-invasive breast cancer cells (rather than abnormal cells), would you be more concerned or less concerned about her screening test result?

(RESPONSE FRAME)

1. More concerned
2. (No difference)
3. Less concerned
4. (Don't know)
5. (Refused)
6. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=3 – Male, Option 3)

D12. And if research shows that watchful waiting is a safe and effective option, how do you think you would prefer your wife, daughter, mother or close female friend manage these pre-invasive breast cancer cells? Would you say...

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)
5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

[PRED13: IF RAND=4, CONTINUE. ELSE GO TO TS4\_SECTION D]

\*(RAND=4 – Male, Option 4)

D13. Breast screening (mammograms) detects pre-invasive breast cancer cells in the breast as well as finding breast cancers. In some women these pre-invasive breast cancer cells can progress to invasive cancer and in others they do not. It's estimated that if left untreated about one-third may progress to breast cancer over 10 years or more. That means that for about two-thirds of women these pre-invasive breast cancer cells may not become cancer

Imagine your wife, daughter, mother or close female friend had a breast screen and follow-up tests showed that there were pre-invasive breast cancer cells found in her breast.

How concerned would you be about her result? Would you say...

[IF NECESSARY: 'Invasive' cancer means potentially life threatening.]

(RESPONSE FRAME) (READ OUT)

1. Extremely concerned
2. Moderately concerned
3. (Neither concerned nor unconcerned)
4. Not really concerned
5. Not concerned at all
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=4 – Male, Option 4)

D14. Pre-invasive breast cancer cells are usually treated by surgery, radiation or drugs as in the case of breast cancer. Another approach is called watchful waiting, where doctors closely monitor the pre-invasive breast cancer cells with regular mammograms and only treat if cells become more invasive.

If research shows that watchful waiting is a safe and effective option, how do you think you would prefer she manage these pre-invasive breast cancer cells? Would you say...

[IF NECESSARY: If people want more information on exactly what watchful waiting would entail - say, that's what research would determine.]

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)
5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(RAND=4 – Male, Option 4)

D15. Thinking again about the previous question and the same person, if these pre-invasive breast cancer cells were now called abnormal cells (rather than pre-invasive cells), would you be more concerned or less concerned about her screening test result?

(RESPONSE FRAME)

1. More concerned
2. (No difference)
3. Less concerned
4. (Don't know)
5. (Refused)
6. (Respondent does not understand terminology / issues) (GO TO TS4)



\*(RAND=4 – Male, Option 4)

D16. And if research shows that watchful waiting is a safe and effective option, how do you think you would prefer your wife, daughter, mother or close female friend manage these abnormal cells? Would you say...

(RESPONSE FRAME) (READ OUT)

1. Definitely prefer treatment
2. Probably prefer treatment
3. (Prefer to do nothing)
4. Probably prefer watchful waiting (close monitoring by doctors)
5. Definitely prefer watchful waiting (close monitoring by doctors)
6. (Don't know)
7. (Refused)
8. (Respondent does not understand terminology / issues) (GO TO TS4)

\*(ALL)

TS4\_Section D

**\*SECTION E: DISEASE DEFINITION**

\*(ALL)

E0. Next, I'd like to ask you a couple of questions about the way diseases are defined.

1. Continue

\*(ALL)

E1. From time to time, doctors who specialise in a particular disease will come together to discuss the characteristics of that disease, to decide who should be diagnosed with it and who requires treatment for it. These are called panels and currently some doctors on these panels HAVE financial ties with pharmaceutical companies who market drugs for that disease and some DO NOT.

Is it appropriate or inappropriate for doctors who HAVE financial ties with pharmaceutical companies to be members of these panels?

PROBE: IS THAT COMPLETELY, MOSTLY OR SLIGHTLY APPROPRIATE / INAPPROPRIATE?

(IF NECESSARY: Financial ties mean do paid work such as being a speaker or a consultant)

(RESPONSE FRAME) (DO NOT READ OUT)

1. Completely appropriate
2. Mostly appropriate
3. Slightly appropriate
4. (Neither appropriate nor inappropriate)
5. Slightly inappropriate
6. Mostly inappropriate
7. Completely inappropriate
8. (Don't know)
9. (Refused)

\*(ALL)

E2. Sometimes, these panels decide to change the definition of a disease in a way that means larger or smaller numbers of people may be treated for it. A recent study found on average, roughly three-quarters of doctors on these panels had financial ties with the pharmaceutical companies selling medicines for the same diseases.

Based on this knowledge, how appropriate or inappropriate is it for doctors with financial ties to pharmaceutical companies who market drugs for that disease to be on these panels?

PROBE: IS THAT COMPLETELY, MOSTLY OR SLIGHTLY APPROPRIATE / INAPPROPRIATE?

(RESPONSE FRAME)

1. Completely appropriate
2. Mostly appropriate
3. Slightly appropriate
4. (Neither appropriate nor inappropriate)
5. Slightly inappropriate
6. Mostly inappropriate
7. Completely inappropriate
8. (Don't know)
9. (Refused)

\*(ALL)

E3. Ideally, what proportion of the panel should be made up of doctors with financial ties to pharmaceutical companies who market drugs for that disease?

(READ OUT)

1. None (0%)
2. A minority - less than 50%
3. A majority - 50% or more
4. (Don't care)
5. (Don't know)
6. (Refused)

\*(ALL)

TS5\_Section E

**\*SECTION F: EXPERIENCE WITH CANCER**

\*(ALL)

F0. We're almost finished. Now I'm going to ask you a few brief questions about your experiences with cancer and cancer screening. Sometimes people can find these questions quite personal or sensitive. If you prefer not to answer any question, please let me know and I will move on.

1. Continue

[PREF1:

IF B1a=1 DISPLAY "have had a PSA test to screen for prostate cancer"

IF B1a=2 DISPLAY "have NOT had a PSA test to screen for prostate cancer"

IF B1a=3 DISPLAY "didn't know if you had been screened for prostate cancer"

IF B1a=4 DISPLAY "would prefer not to say if you had been screened for prostate cancer"

IF B2a=1 DISPLAY "have had a mammogram to screen for breast cancer"

IF B2a=2 DISPLAY "have NOT had a mammogram to screen for breast cancer"

IF B1a=3 DISPLAY "didn't know if you had been screened for breast cancer"

IF B1a=4 DISPLAY "would prefer not to say if you had been screened for breast cancer"]

\*(ALL)

F1. Earlier you mentioned that you < have had a PSA test to screen for prostate cancer / have NOT had a PSA test to screen for prostate cancer / didn't know if you had been screened for prostate cancer / would prefer not to say if you had been screened for prostate cancer / have had a mammogram to screen for breast cancer / have NOT had a mammogram to screen for breast cancer / didn't know if you had been screened for breast cancer / would prefer not to say if you had been screened for breast cancer>.

Have you been screened for other forms of cancer?

1. Yes
2. No
3. (Don't know)
4. (Refused)

\*(ALL)

F2a. Have you ever been diagnosed with cancer?

1. Yes
2. No (GO TO F3a)
3. (Don't know) (GO TO F3a)
4. (Refused) (GO TO F3a)

\*(IF F2a=1 – has been diagnosed with cancer)

F2b. What type of cancer?

(ACCEPT MULTIPLES) (DO NOT READ OUT UNLESS REQUIRED)

1. Bowel
2. Breast
3. Cervical
4. Lung
5. Lymphoma
6. Melanoma
7. Prostate
8. Response Given (Specify) \*(PROGRAMMER NOTE: Set up as full verbatim)
9. (Don't know)
10. (Refused)

\*(ALL)

F3a. Have any of your immediate family, that is your parents, siblings or children, ever been diagnosed with cancer?

1. Yes
2. No (GO TO TS6\_Section F)
3. (Don't know) (GO TO TS6\_Section F)
4. (Refused) (GO TO TS6\_Section F)

\*(IF F3a=1 – has a family history of cancer)

F3b. What's their relationship to you?

(SELECT MULTIPLE)

1. Mother
2. Father
3. Sister
4. Brother
5. Daughter
6. Son
7. (Don't know / can't say)
8. (Refused)

\*(IF F3a=1 – has a family history of cancer)

F3c. What type or types of cancer were they diagnosed with?

(ACCEPT MULTIPLES) (DO NOT READ OUT UNLESS REQUIRED)

1. Bowel
2. Breast
3. Cervical
4. Lung
5. Lymphoma
6. Melanoma
7. Prostate
8. Response Given (Specify) \*(PROGRAMMER NOTE: Set up as full verbatim)
9. (Don't know)
10. (Refused)

\*(ALL)

TS6\_Section F

**\*SECTION G: DEMOGRAPHICS**

\*(ALL)

G0. Now I would like to ask you a few demographic questions to make sure we speak with a good cross-section of the community. Again, I'd like to assure you that everything you tell me today is anonymous.

\*(ALL)

G1. Are you of Aboriginal and/or Torres Strait Islander origin?

1. Yes
2. No

\*(ALL)

G2. What is the main language you speak at home?

1. English
2. Other (specify\_\_\_\_\_)

\*(ALL)

G5. What is your employment status?

1. Permanent or on-going
2. Casual/temporary (with no paid sick or annual leave)
3. Fixed-term contract
4. Self-employed
5. (On paid leave: e.g. maternity leave)
6. Unemployed (e.g. looking or not looking for work)
7. Not working / not in the labour force (e.g. student, home duties, retired)

\*(ALL)

G6. Are you now or have you ever worked as a health professional? This includes Doctors, Specialists, Nurses or Pharmacists.

1. Yes
2. No

\*(ALL)

G7. What is the highest level of education that you have completed?

(INTERVIEWER NOTE: Prompt if year 12 or below: Have you completed TAFE, trade or apprenticeship qualifications?)

(RESPONSE FRAME]

1. Postgraduate Degree
2. Graduate Diploma/Graduate Certificate
3. Bachelor Degree
4. Advanced Diploma/Diploma
5. Certificate III/IV
6. Certificate I/II
7. Certificate not further defined
8. Year 12
9. Year 11
10. Year 10 or below
11. Level not determined
98. (Don't know)
99. (Refused)

\*(ALL)

TS7\_Section G

**\*SECTION H: DUAL FRAME WEIGHTING**

[PRESMP1 IF SAMPLE=LANDLINE CONTINUE, ELSE GO TO PRESMP3]

\*(LANDLINE SAMPLE)

SMP1. How many residential phone numbers do you have in your household, not including lines dedicated to faxes, modems or business phone numbers? Do not include mobile phones.

(IF NECESSARY: How many individual LANDLINE numbers are there at your house that you can use to make and receive telephone calls?)

1. Number of lines given (Specify\_\_\_\_\_) RECORD WHOLE NUMBER (ALLOWABLE RANGE 1 TO 99) \*(DISPLAY "UNLIKELY RESPONSE" IF = >3)
2. Don't know/ Not stated (PROGRAMMER NOTE: RECORD IN DATA AS 999)
3. Refused (PROGRAMMER NOTE: RECORD IN DATA AS 888)

\*(LANDLINE SAMPLE)

SMP2 Do you also have a working mobile phone?

1. Yes (GO TO SMP5)
2. No (GO TO SMP5)
3. (Don't know) (GO TO SMP5)
4. (Refused) (GO TO SMP5)

[PRESMP3 IF SAMPLE=MOBILE CONTINUE, ELSE GO TO SMP5]

\*(MOBILE SAMPLE)

SMP3 Is there at least one working fixed line telephone inside your home that is used for making and receiving calls?

1. Yes
2. No (GO TO SMP5)
3. (Don't know) (GO TO SMP5)
4. (Refused) (GO TO SMP5)

\*(SMP3=1 - MOBILE SAMPLE, HAS AT LEAST ONE WORKING FIXED LINE IN HOUSEHOLD)

SMP4 How many residential phone numbers do you have in your household, not including lines dedicated to faxes, modems or business phone numbers. Do not include mobile phones.

(IF NECESSARY: How many individual LANDLINE numbers are there at your house that you can use to make and receive telephone calls?)

1. Number of lines given (Specify\_\_\_\_\_) RECORD WHOLE NUMBER (ALLOWABLE RANGE 1 TO 99) \*(DISPLAY "UNLIKELY RESPONSE" IF = >3)
2. Don't know/ Not stated (PROGRAMMER NOTE: RECORD IN DATA AS 999)
3. Refused (PROGRAMMER NOTE: RECORD IN DATA AS 888)

\*(ALL)

SMP5 And how many people in your household are aged 18 years or over?

1. One
2. Two or more (Specify) [ALLOWABLE RANGE 2-6]
3. (Don't know)
4. (Refused)

\*(ALL)

TELDUM (COMPUTE TELEPHONE STATUS)

1. Mobile only (SMP3=2,3,4)
2. Landline only (SMP2=2,3,4)
3. Dual user (SMP2=1 or SMP3=1)

**\*CLOSE & RECONTACT**

\*(ALL)

CLOSE0: This brings us to the end of the survey questions. Just before we finish...

1. Continue

\*(ALL)

REC1. The University of Sydney are planning to conduct another telephone survey, with similar questions to the ones you answered today, within the next 12 months. Would you be interested in being a potential participant in this future study?

(IF NECESSARY: Saying "yes" at this stage means you may be invited, but you will not be obliged to participate)

1. Yes (GO TO REC2)
2. No (GO TO END1a)

\*(REC1=1 – agrees to recontact)

REC2. And can I confirm that you consent to the Social Research Centre passing your contact details (name and telephone phone number) and survey responses to Sydney University so that they will be able to contact you for the future study?

(IF NECESSARY: All of your information will be sent securely to the University of Sydney researchers and used for research purposes only. Survey responses would need to be passed on to the University of Sydney to enable re-contact based on views and experiences)

1. Yes (GO TO REC3name)
2. No (GO TO END1a)

\*(REC2=1 – Agrees to recontact &amp; to passing of details and responses)

REC3name Can you please tell me your name?

1. (Specify\_\_\_\_\_)

REC3telnum. Is this the phone number you'd like the researchers to contact you on? (If no: can you please tell me a preferred phone number?)

1. Yes
2. No – ENTER NEW TELNUM (INCLUDE AREA CODE)

RECaltnum As this survey will be conducted sometime over the next 12 months, do you have an alternative number you could give us (such as a mobile phone), just in case we can't reach you on this phone number?

1. Yes – ENTER ALTERNATE NUM (INCLUDE AREA CODE)
2. No

\*(ALL)

END1a. And finally, is overdiagnosis something you would like to know more about?

1. Yes (GO TO END1B)
2. No (GO TO END2)
3. (Don't know) (GO TO END2)
4. (Refused) (GO TO END2)

\*(IF End1a=1 – Yes would like to know more)

END1b. You can find more information on the not-for-profit website 'Preventing Overdiagnosis', at [www.preventingoverdiagnosis.net](http://www.preventingoverdiagnosis.net)



1. Continue

\*(ALL)

END2. Thank you for your involvement in this survey. All of the information you provided today will be kept secure and only used for research purposes.

Just in case you missed it my name is (...) and this survey was conducted on behalf of Bond and Sydney Universities. If you have any questions there is a phone number I can give you if you like.....

1. Wants contact details (GO TO END3)
2. Does not want contact details (GO TO CLOSE1)

\*(END2=1 - WANTS CONTACT DETAILS)

END3.

Questions about who is conducting the survey and how your telephone number was obtained:  
The Social Research Centre, Phone: 1800 023 040

Questions concerning the manner in which this research is being conducted - Bond University Human Research Ethics Committee, c/o Bond University Office of Research Services. Bond University, Gold Coast, 4229 Phone: +61 7 5595 4194 Fax: +61 7 5595 1120 Email: [buhrec@bond.edu.au](mailto:buhrec@bond.edu.au)

If you have any queries or would like to be informed about the summary of research findings, please contact: Jenny Doust (Principal Investigator) Centre for Research in Evidence-Based Practice, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia, 4229, Phone: 07 5595 5518; Email: [jdoust@bond.edu.au](mailto:jdoust@bond.edu.au)

Cancer Council National Helpline:131120

\*(ALL)

**CLOSE1. Thank you very much for your time.**

\*(ALL)

TS8\_CLOSE

**\*TERMINATION SCRIPTS**

TERM1. Thank you anyway but we need to speak with people who are aged 18 years and over.

TERM2. Thank you for your time.

**ALLTERM**

| <b>Code</b> | <b>Definition</b> | <b>Description</b>           | <b>SUR category</b> |
|-------------|-------------------|------------------------------|---------------------|
| 1           |                   | Completed interview          | Interview           |
| 2           | INTRO2a=3         | Household refusal            | Refusal             |
| 3           | INTRO2a=4         | Language other than English  | Screen out          |
| 4           | INTRO2a=6         | No one aged 18+ in household | Screen out          |
| 5           | INTRO2b=3         | Mobile answerer refusal      | Refusal             |
| 6           | INTRO2b=4         | Language other than English  | Screen out          |
| 7           | INTRO2b=6         | Under 18 years               | Screen out          |
| 8           | MOB2=3            | Respondent refusal           | Refusal             |
| 9           | MOB_APPT=3        | Respondent refusal           | Refusal             |
| 10          | INTRO3a=3         | Respondent refusal           | Refusal             |
| 11          | INTRO3a=4         | Language other than English  | Screen out          |
| 12          | INTRO3b=3         | Respondent refusal           | Refusal             |
| 13          | All other         | Midway termination           | Refusals            |